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Dhshan Hassan Dhshan

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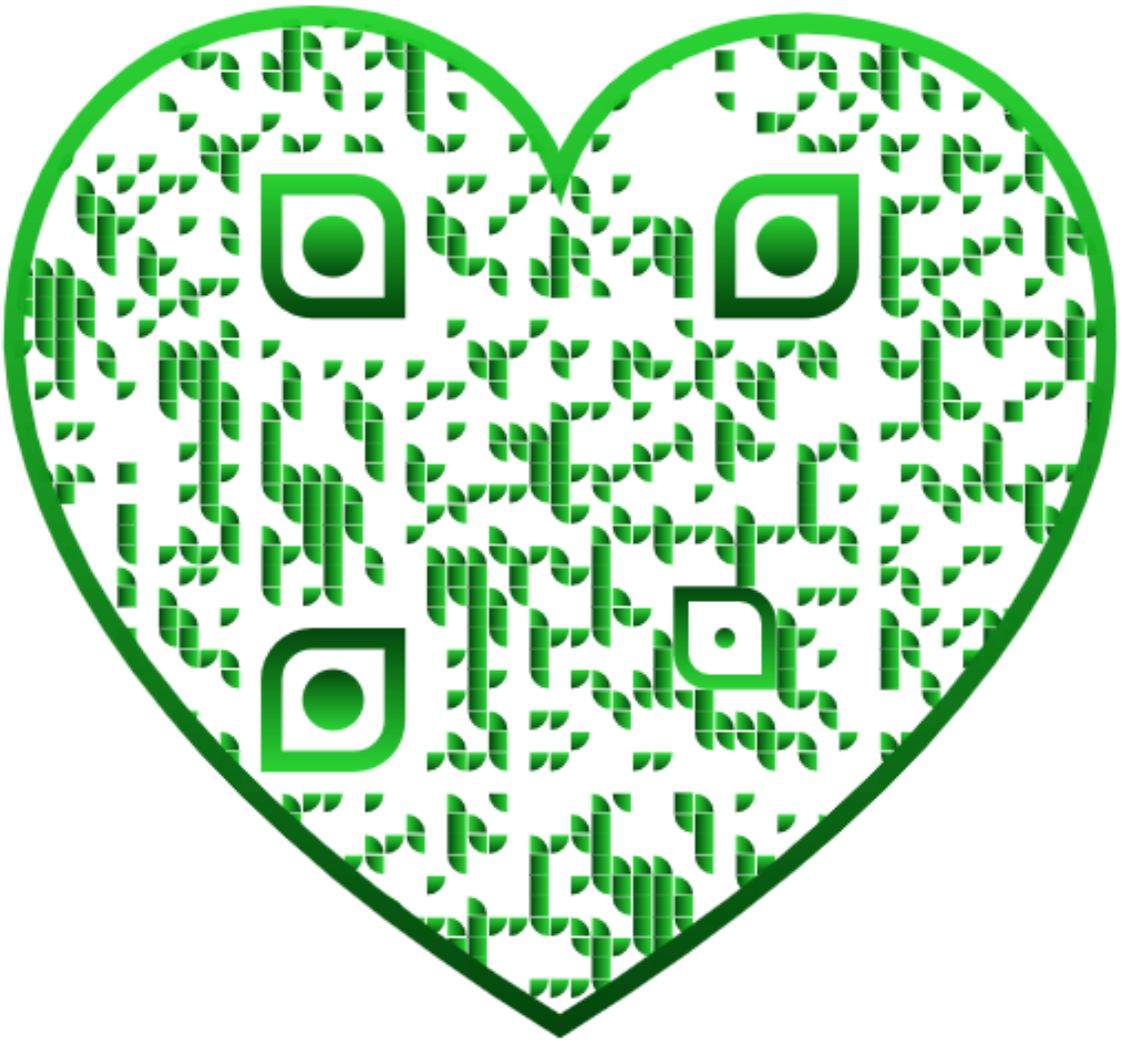

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Pharmacy Practice for Postgraduate

Dhshan Hassan Dhshan

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For Contact

/Dr.Dhshan
/Pharma.Guide.book
/DhshanPharma
Dr.Dhshan@Gmail.com
011 2222 81 83 (Customer Service), 0100 86 99 85 6 (Dhshan)

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أخي العزيز: إن ظهر لك خطأ طباعي أثناء قراءتك للكتاب فأرسله لنا عبر البريد الخاص بالمؤلف

Dr.Dhshan@Gmail.com

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حتى نتداركه فى الطباعات اللاحقة، وبهذا تكون قد شاركت معنا بجهد مشكور يتضافر مع جهدنا جميعا فى سيرنا نحو الأفضل والأكمل ..

هل كتاب Pre-Work Pharma Guide المخصص للخريجين .. مفيد لي؟

- عزيزي المقبل على شراء هذا الكتاب: إن هذا الكتاب صمم بعناية **للخريجين** المقبلين على سوق العمل ليساعدهم من خلال **تذكيرهم** بالمجموعات الدوائية، والأسماء التجارية، والفروقات الهامة بين كل مجموعة وآخرى، أو دواء وآخر بنفس المجموعة، والوصف الأولي لكل دواء، وأهم الأعراض الجانبية، والتداخلات الدوائية، والجرعات، وأهم ما يميز الكتاب هو شرح كيفية تقديم المشورة الصيدلانية للمجموعات الدوائية لوصف الدواء **Patient Counselling**.

- صمم الكتاب ليسهل للخريج خلال فترة زمنية وجيزة (**45 يوم**) سرعة الانخراط في مجال العمل الدوائي.

- لا يُنصح إطلاقاً باقتناء هذا الكتاب **للطلاب** دارسى علم الفارماكولوجى كعلم أكاديمي .. اقتناؤك لهذا الكتاب فى مرحلة الدراسة بالجامعة يبعدك عن تعلم أساسيات علم الفارماكولوجى ولا ينصح بهذا، لأن تعلم الأساسيات بشكل سليم داخل المرحلة الجامعية يجعلك تكمل تعليمك بعد التخرج بكل سهولة.

- كتاب **Pre-Work** مصمم بعناية فائقة فيصعب علينا أن نختصر المحتوى العلمى أكثر من ذلك حتى لا يختل المفهوم العلمى، ولا يمكن أن نقوم بزيادة المحتوى أكثر من ذلك فيختل هدف الكتاب فى سرعة الانخراط بالعمل.

- يوميات **Pre-Work** متوفرة الآن مجاناً على اليوتيوب وتطبيق فارما تيوب، وهي عبارة عن 45 فيديو يتم شرح الكتاب حسب الجدول المنظم لمذاكرة الكتاب (**Study Timeline Table**)، الفيديوهات تتوفر بعنوان **Pharma Tube Pre-Work**.

- **تحذير**: تعريب المحتوى العلمي للكتاب أو اختصاره بواسطة الآخرين لإنشاء محتوى مشابه .. من المحتمل أن يؤدى الى خلل فى إيصال المعلومة للمتلقى، فقد تصل ناقصة غير مكتملة الفهم أو تفهم بطريقة خاطئة، عوضاً على احتمالية إساءة استخدام المحتوى المعرب بواسطة غير المختصين "الدخلاء".

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تعريب الكتاب وإخراج المحتوى العلمى بداخلة بأى وسيلة كتابية أو الكترونية يعرضك للمساءلة القانونية

- الآن:

- يمكنك متابعة فيديوهات **فارما تيوب** مجاناً، والتى تتضمن شرح علم الفارماكولوجي الأساسي والسريري والفارماكوثيرابى، وذلك من خلال هاتفك عبر تحميل تطبيق "**فارما تيوب**" او "**Pharma Tube**" وتنضم الى أكثر من مليون ونصف مستخدم للتطبيق (متوفر على جوجل بلاي و آب ستور).

- يمكنك تحميل تطبيق "**Pharma Guide MCQs**" مجاناً من جوجل بلاى واختبر نفسك فى أكثر من 1000 سؤال تطبيقي مقدم من فارما جايد.

"**لا نبتكر المعلومة، ولكننا نبتكر طريقة لجعلها سهلة**"

"We don't discover the **text**, but discover a **way** to make it **easy** "

- فارما جايد ليس مجرد كتاب، فهو منظومة شاملة تلبى جميع احتياجاتك فى مجال علم الفارماكولوجي:

الرفيق: يحقق كتاب **Pharma Guide Original** (**الإصدار الرابع**) المعادلة الصعبة، فهو يجمع بين علم الفارماكولوجي الأساسي (Basic)، والسريري (Clinical)، مع إضافة Pharmacotherapy من رصد التوصيات (Recommendations)، و التوجيهات العلاجية (Guidelines)، ليصبح هذا الكتاب هو الرفيق لك دائماً فى جميع مراحل تعليمك، بداية من الجامعة وحتى بعد تخرجك (مثل: مذاكرة البورد الأمريكي او Pharm-D).

الشرح: نوفر شرحاً كاملاً مجاناً للكتب (**Original** + **Pre-Work** + **Cosmo-Spot**) عن طريق قناة **فارما تيوب** على اليوتيوب او تطبيق فارما تيوب (**Pharma Tube**)، ليصل عدد ساعات التسجيل الي أكثر من 250 ساعة من الشرح.

الأسئلة: نوفر كتاب **Pharma Guide MCQs** يحتوي على 1200 سؤال تطبيقي واسئلة المعادلات الكندية والأمريكية.

المراجعة: من الصعوبة فى علم الفارماكولوجي هو ربط المجموعات الدوائية بعضها البعض، فدائماً نشعر بعد الإنتهاء من المذاكرة بالنسيان وصعوبة فى ربط الموضوعات، لذلك وفرنا كتاب **Pharma Guide Mind Map**، الكتاب المبتكر ليجمع الفارما كلها فى 45 خريطة ذهنية، ليصبح الكتاب الأمثل للمذاكرة قبل الإمتحان.

بعد التخرج: الجميع يريد الحصول على عمل بعد التخرج، ويتطلب منه الأمر مراجعة سريعة للفارما، هذة المراجعة تقوم بالتركيز على الناحية العلمية/العملية فى اقصر فترة زمنية ممكنة، وهذا ما يوفرة كتاب الخريجين المقدم من فارما جايد **Pharma Guide Pre-Work**، الكتاب المبتكر المختصر بحرص ومرتب بإتقان، كما وفرنا ايضاً كتيب التجميل **Pharma Guide Cosmo-Spot** ليكون الإنطلاقة لك فى عالم مستحضرات التجميل.

المطورون: المطورون هم محبون ومتابعون لفارما تيوب وفارما جايد على مستوى العالم نتجمع سوياً من خلال جروب "المطورون" على فيس بوك **Pharma Guide Developers** ويتم وضع الاقتراحات والأفكار لتنفيذها، سوف نكون سعداء بإنضمامك إلينا

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- **عن المؤلف**: هو الصيدلي **دهشان حسن دهشان** خريج صيدلة الأزهر- القاهرة عام 2013 وبدأ العمل على فارما تيوب و فارما جايد منذ عام 2011.

شكراً لعائلتي، للأساتذتي، لأصدقائي، وشكراً لك ايضاً على ثقتك فى اعمالنا مع تمنياتي بالنجاح والتوفيق .. دهشان حسن دهشان

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Book Symbol Guide

#	Important	##	Very Important
####	Very-very Important	> or <	Higher or lower
>>	Very higher or more details		
CAPITAL	Very-very Important, *like*; ***Aminoglycosides***; **OTOTOXICITY**		
3rd Generation Cephalosporins			Drug Class Shading Colour
Parenteral			Sub-Class Shading Colour
Ceftriaxone (Rocephin®)#			Generic/Brand Shading Colour
Ceftriaxone			Generic Name Colour
Rocephin®			Brand Name Colour
Ex.☞ **Typhoid fever** and **meningitis**			Therapeutic Uses colour

Study Timeline Table

* **Steps to Complete Pre-Work Study**;

1) ***Open*** **Pharma Guide Pre-Work book** and ***study*** **topics** in **Day 1** in this **table**.
2) ***Open*** **Check Yourself** ***chapter*** in the **end** of *your day* and **evaluate yourself.**
3) ***If*** your **correct answers** are; **≥ 3 questions** *from* **5** "***mark*** in this table; **Good**).
4) ***If*** your **correct answers** are; **< 3 questions** *from* **5** "***mark*** in this table; **Need Revision**).
5) In **pharmacy practice** ***column*** in this **table**; you need to **work** in the **Pharmacy** to ***complete*** **it** by *yourself*.

رابط الشرح على اليوتيوب

Day	Topics	QR	Pre-Work Questions	Pharmacy Practice
1	Antibiotics Introduction β-lactam Antibiotics		❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved
2	Non-β-lactam Antibiotics Antibiotics Disrupt Cell Membrane Antibiotics Inhibits Protein Synthesis		❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved
3	Quinolones and Fluoroquinolones Sulfonamides Anti-Mycobacterial		❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved
4	Antifungal Drugs Antiviral Drugs Antiparasitic Drugs		❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved
5	Revision		❑ Good (≥ 3/5)	
6	Drugs for Peptic Ulcer Disease Promotility (Prokinetic) Agents		❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved
7	Antiemetic Agents Antidiarrheal Agents Laxatives		❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved
8	Drugs for IBS Drugs for IBD Pancrelipase and Drugs for Gallstones		❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved
9	Revision		❑ Good (≥ 3/5)	
10	Antihistamines		❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved
11	Drugs for Asthma and COPD		❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved

12	Allergic Rhinitis Medications Cough Medications Respiratory Tract Infections (RTIs)		❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved
13	Revision		❑ Good (≥ 3/5)	.....
14	Drugs for Sexual Dysfunction Sexual Transmitted Disease Regimens		❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved
15	Drugs for Kidney Stones Drugs for Benign Prostatic Hyperplasia Drugs for Urinary Incontinence Urinary Tract Infections (UTIs)		❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved
16	Revision		❑ Good (≥ 3/5)	.....
17	NSAIDs Paracetamol		❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved
18	Opioid Analgesics Skeletal Muscles Relaxants		❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved
19	Drugs for Gout and Hyperuricemia Disease Modifying Antirheumatic Drugs		❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved
20	Drugs for Osteoarthritis Drugs for Osteoporosis		❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved
21	Revision		❑ Good (≥ 3/5)	.....
22	Diuretics Antihypertensive Drugs		❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved
23	Antihypotensive Drugs Antianginal Drugs Drugs for Heart Failure (HF)		❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved
24	Antiarrhythmic Drugs		❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved
25	Antithrombotic & Antihemorrhagic Drugs		❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved
26	Antihyperlipidemic Agents Drugs for Varicose Veins & Haemorrhoids		❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved
27	Revision		❑ Good (≥ 3/5)	.....
28	Sedative-Hypnotic Drugs		❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved
29	Antidepressant Drugs & Lithium Therapy		❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved

30	Psychostimulant Drugs Antipsychotic Drugs	❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved
31	Drugs for Neurodegenerative Diseases	❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved
32	Antiepileptic Drugs	❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved
33	Headache Managements General Anesthetics & Local Anesthetics	❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved
34	**Revision**	❑ Good (≥ 3/5)	
35	Hypothalamic-Pituitary Hormones Thyroid and Antithyroid Drugs	❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved
36	Adrenocortical Hormones Insulin and Antidiabetic Drugs	❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved
37	Gonadal Hormones Hormonal Contraceptives	❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved
38	**Revision**	❑ Good (≥ 3/5)	
39	Cancer Chemotherapy	❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved
40	Immunosuppressants	❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved
41	Hematopoietic Drugs	❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved
42	**Revision**	❑ Good (≥ 3/5)	
43	Acne Vulgaris (AV) Dermatitis and Sunburn	❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved
44	Skin Aging and Wrinkles Hyperpigmentation Psoriasis and Vitiligo	❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved
45	Cold Sores, Shingles and Warts Cellulitis and Erysipelas Scabies/Lice and Tinea Infections Hair loss (Alopecia)	❑ Good (≥ 3/5) ❑ Need Revision (< 3/5)	❑ Achieved ❑ Not achieved

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Antimicrobial Agents

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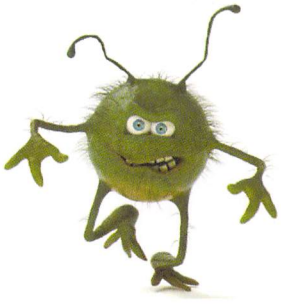


Introduction

➢ Types of Organisms:-

A) Eukaryotic; is ***any* organism** whose **cells** *have* a **nucleus** and ***other organelles*** *enclosed within* **membranes**. **Eukaryotic cells** *such as* in **Animal**, **Plant**, **Fungal** and **Protista cells**;

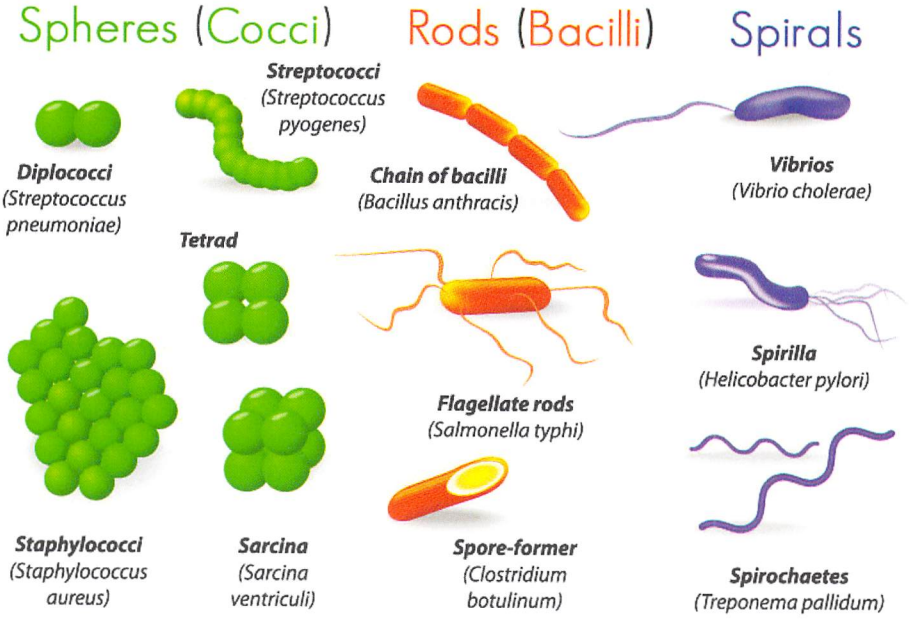
- **Cell wall**; Only in plant cells and fungi.
- **Ribosome** (**80S**); Small subunit (40S) and large subunit (60S).

B) Prokaryotic; is a ***unicellular* organism** that *lacks* a **nucleus**, **mitochondria**, or ***any other* membrane-bound organelle**; **Prokaryotic cells** *such as* in **Bacteria** and **Archaea cells**;

- **Cell wall**; Present and complexed.
- **Ribosome** (**70S**); Small subunit (30S) and large subunit (50S).

C) Virus; is a ***small infectious* agent** that **replicates *only* inside** the **living cells** of ***other organisms***; They *lack* both a cell wall and a cell membrane, and they do not carry out metabolic processes.

➢ Shapes and Arrangements of Bacteria:-

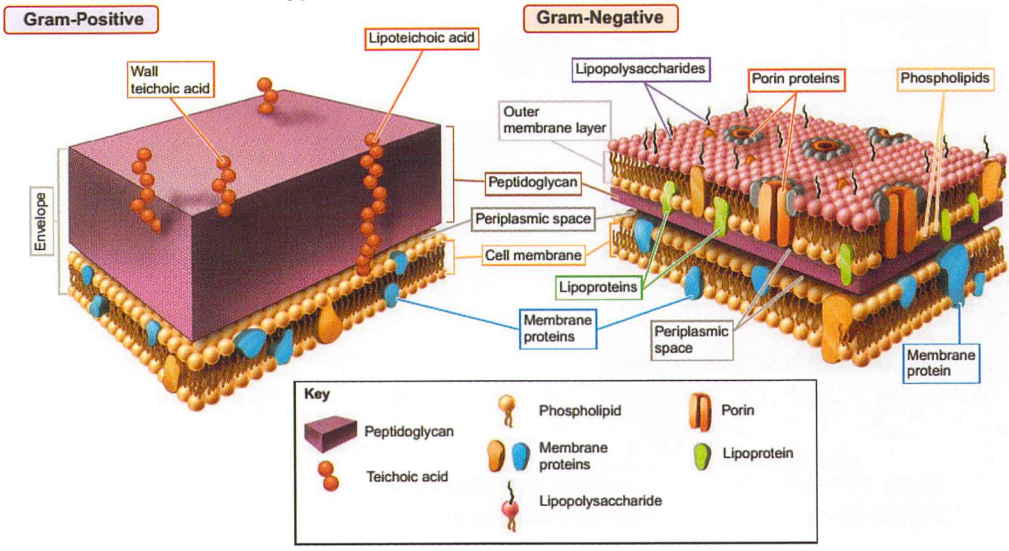


➢ Gram Stain:-

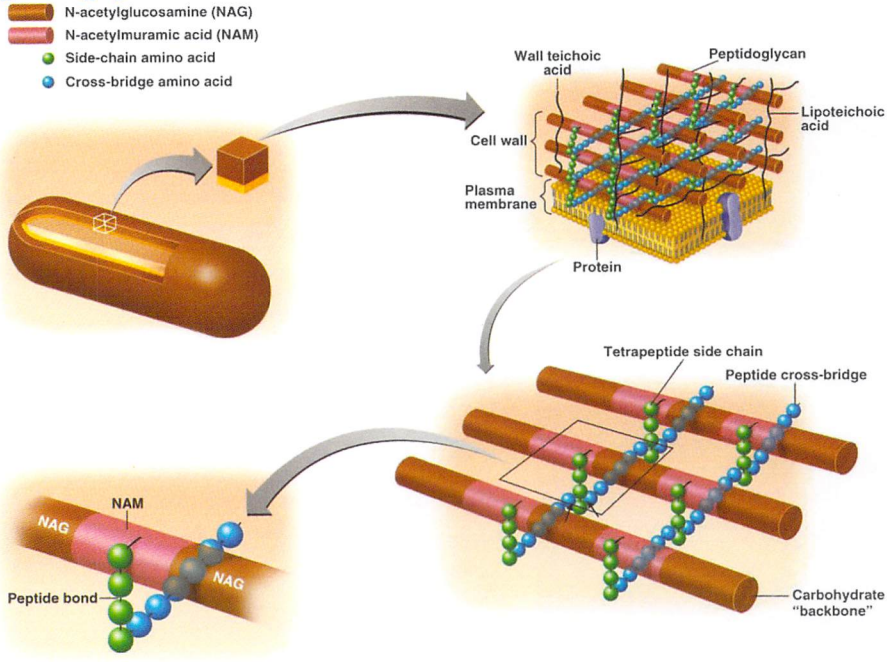
- The name comes from the *Danish bacteriologist* **Hans Christian Gram**, who developed the technique in 1884.
- **Gram stain** is a ***method*** of **staining** used to ***differentiate*** **bacterial species** into **two *large* groups**; **Gram +ve** (violet colour; crystal violet) & **Gram -ve** (pink colour; safranin).
- Gram staining ***differentiates*** **bacteria** by the chemical and physical properties of their **cell walls**; by *detecting* **Peptidoglycan**.
- **Gram positive bacteria**; **thick layer** of **peptidoglycan** (*about* 90% of cell wall).
- **Gram negative bacteria** (**thin layer** of **peptidoglycan** (*about* 10% of cell wall).

➢ Bacterial Cell Wall:-

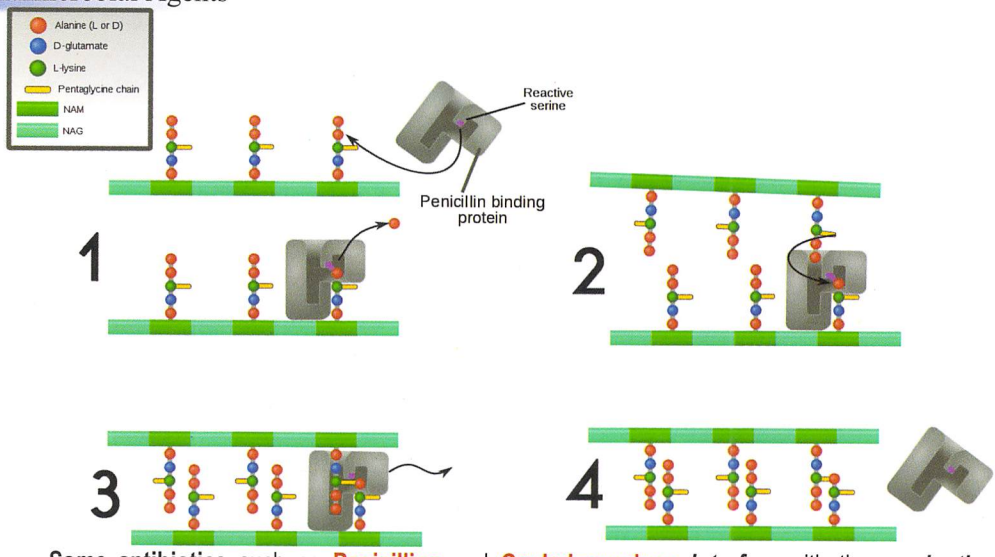
- There are **two *main types*** of **bacterial cell walls**; **gram-positive** and **gram-negative**.



➢ Peptidoglycan:-



- **Peptidoglycan** is ***made up*** of a **polysaccharide backbone** consisting of alternating **N-Acetylmuramic acid** (**NAM**) & **N-Acetylglucosamine** (**NAG**) residues in **equal amounts**.
- **Peptidoglycan** is ***responsible for*** the ***rigidity*** of the **bacterial cell wall** and for **cell shape**.
- **Penicillin-binding proteins** (**PBPs**) are a ***normal constituent*** of **many bacteria**, which are ***essential for*** **final stage** of **bacterial cell wall *synthesis*** (form the **bonds *between*** **oligopeptide *crosslinks*** in **peptidoglycan**).
- **PBPs** are ***members*** of a **subgroup** of **enzymes *called*** **Transpeptidases**.



- ***Some*** **antibiotics** such as **Penicillins** and **Cephalosporines** ***interfere*** with the ***production*** of **peptidoglycan** by ***binding to*** **penicillin-binding proteins enzymes (Transpeptidases enzymes).**

➢ Classification of Bacteria:-

- ***According to*** **Gram** ***stain*** (<u>most</u> <u>common</u>);

Gram Positive Bacteria

Cocci

Staphylococcus spp.
Streptococcus spp.
Enterococcus spp.

Bacilli (Rods)

Non-Spore Forming (Aerobic)

Corynebacterium spp.
Erysipelothrix spp.
Nocardia spp.

Non-Spore Forming (Anaerobic)

Propionibacterium spp.
Actinomyces spp.
Listeria spp.
Lactobacillus spp.
Peptostreptococcus spp.
Bifidobacterium spp.

Spore-forming (Aerobic)

Bacillus spp.

Spore forming (Anaerobic)

Clostridium spp.

Atypical

(**Bacteria** that ***do not*** **color** with **gram-staining**)

Chlamydia
Mycoplasma
Rickettsia

Mycobacteria

(***Mycobacteria*** a genus of ***rod-shaped*** **acid-fast bacteria** having ***two significant*** **pathogenic species**)

- ***Mycobacterium leprae***; **leprosy.**
- ***Mycobacterium tuberculosis***; **tuberculosis.**

Gram Negative Bacteria

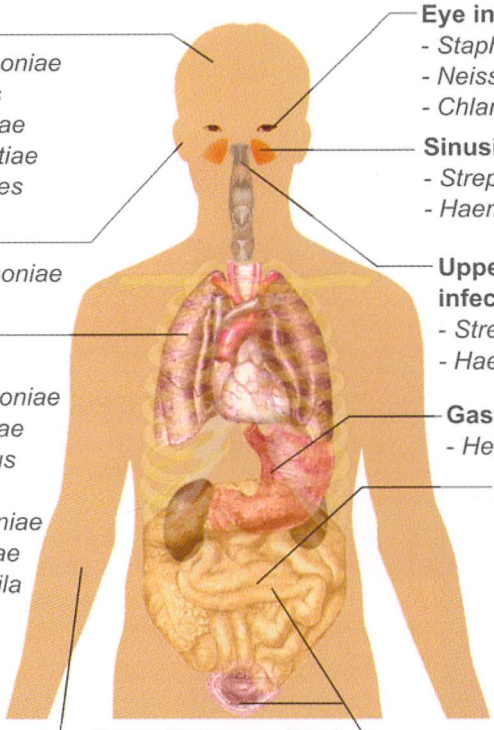
Cocci

Neisseria gonorrhoeae
Neisseria meningitidis

Bacilli (Rods)

Escherichia coli
Vibrio cholerae
Klebsiella spp.
Salmonella spp.
Shigella spp.
Proteus spp.
Pseudomonas aeruginosa
Helicobacter pylori
Legionella pneumophila
Haemophilus influenza
Brucella spp.
Bordetella pertussis

- ***According to site of infection***;



Bacterial meningitis
- *Streptococcus pneumoniae*
- *Neisseria meningitidis*
- *Haemophilus influenzae*
- *Streptococcus agalactiae*
- *Listeria monocytogenes*

Otitis media
- *Streptococcus pneumoniae*

Pneumonia
Community-acquired:
- *Streptococcus pneumoniae*
- *Haemophilus influenzae*
- *Staphylococcus aureus*

Atypical:
- *Mycoplasma pneumoniae*
- *Chlamydia pneumoniae*
- *Legionella pneumophila*

Tuberculosis
- *Mycobacterium tuberculosis*

Skin infections
- *Staphylococcus aureus*
- *Streptococcus pyogenes*
- *Pseudomonas aeruginosa*

Sexually transmitted diseases
- *Chlamydia trachomatis*
- *Neisseria gonorrhoeae*
- *Treponema pallidum*
- *Ureaplasma urealyticum*
- *Haemophilus ducreyi*

Eye infections
- *Staphylococcus aureus*
- *Neisseria gonorrhoeae*
- *Chlamydia trachomatis*

Sinusitis
- *Streptococcus pneumoniae*
- *Haemophilus influenzae*

Upper respiratory tract infection
- *Streptococcus pyogenes*
- *Haemophilus influenzae*

Gastritis
- *Helicobacter pylori*

Food poisoning
- *Campylobacter jejuni*
- *Salmonella*
- *Shigella*
- *Clostridium*
- *Staphylococcus aureus*
- *Escherichia coli*

Urinary tract infections
- *Escherichia coli*
- Other Enterobacteriaceae
- *Staphylococcus saprophyticus*
- *Pseudomonas aeruginosa*

➢ Mechanism of Bacterial Resistance:-

- **Enzymatic Inactivation**;
  - **β-lactamase enzyme** (**Penicillinase**) which ***inactivate*** **Penicillin** and ***other*** **β-lactam antibiotics** by ***hydrolysis*** of **β-lactam ring**.
- **Impermeability** *to* **Antibiotic**;
  - ***Many*** **antibiotics** ***enter*** the **cell** *through* **protein channels** called "**Porin**" ***absence*** or ***mutation*** or ***loss*** of a **porins channel** can ***slow*** the **rate** of drug ***entry*** *into a* **cell** or ***prevent*** **entry**.
- **Efflux**;
  - **Bacteria** also have **efflux pumps** that can ***transport*** **drugs** ***out*** of the **cell** (*common mechanism in* **Gram -ve**).
- **Mutation**; is a ***change*** in the **DNA** that can ***sometimes cause***;
  - ***Decrease*** **affinity** *of* **target enzyme**.
  - ***Alteration*** *of* **target site**.
  - ***Over production*** *of* **target site** *or* **metabolite**.

➢ Classification of Antibiotics:-

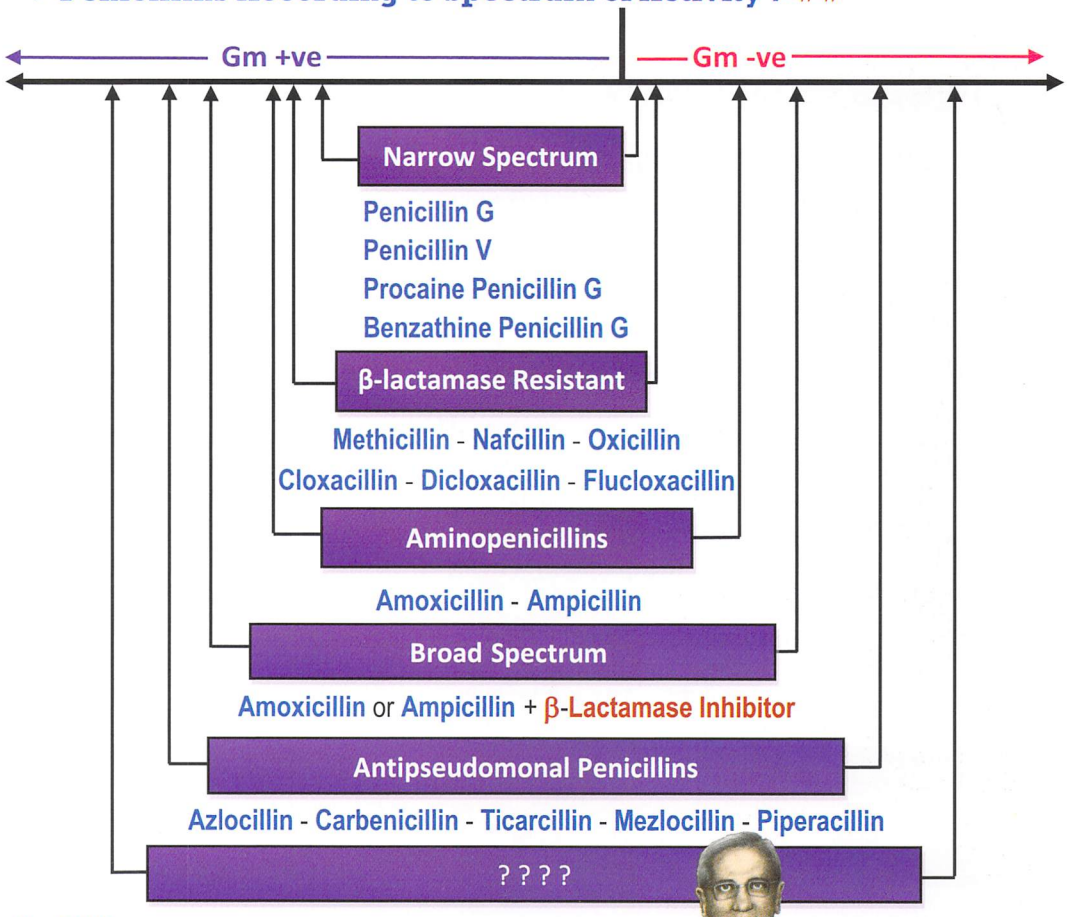
Inhibit		Classification		Antibiotics				
Cell Wall Synthesis	Beta Lactams	Penicillins	Natural Penicillins	Penicillin G	Penicillin V			
				Procaine Penicillin G	Benzathine Penicillin G			
			Antistaphylococcal Penicillins	Methicillin	Nafcillin	Oxacillin		
				Cloxacillin	Dicloxacillin	Flucloxacillin		
			Aminopenicillins	Ampicillin	Amoxicillin			
			Broad Spectrum Penicillins	Ampicillin/Sulbactam	Sultamicillin			
				Co-Amoxiclav (Amoxicillin/Clavulanate)				
			Anti-Pseudomonal Penicillins	Carboxypenicillins	Ticarcillin	Carbenicillin		
				Ureidopenicillins	Piperacillin	Mezlocillin	Azlocillin	
				Combination	Ticarcillin/Clavulanate			
					Piperacillin/Tazobactam			
		Cephalosporins	1st Generation	Cefadroxil	Cephalaxin	Cephradine	Cefazolin	
			2nd Generation	Cefaclor	Cefuroxime	Cefprozil	Cefoxitin	
			3rd Generation	Ceftriaxone	Cefotaxime	Cefoperazone		
				Ceftazidime	Ceftazidime/Avibactam			
				Cefixime	Cefdinir	Cefpodoxime	Cefditoren	
			4th Generation	Cefepime	Cefpirome			
			5th Generation	Ceftobiprole	Ceftaroline	Ceftolozane/Tazobactam		
		Monobactams		Aztreonam				
		Carbapenems		Imipenem/Cilastatin	Meropenem	Doripenem	Ertapenem	
	Non-β-lactams	Glycopeptide Antibiotics		Vancomycin	Teicoplanin	Telavancin		
				Dalbavancin	Oritavancin			
		Others		Fosfomycin	Bacitracin	Cycloserine		
Cell Membrane				Colistin	Daptomycin			
Protein Synthesis	30S	Tetracyclines		Tetracycline	Oxytetracycline	Doxycycline	Minocycline	
		Glycylcyclines		Tigecycline				
		Aminoglycosides		Streptomycin	Neomycin	Amikacin	Gentamicin	Tobramycin
	50S	Macrolides		Erythromycin	Clarithromycin	Azithromycin	Spiramycin	Josamycin
		Ketolides		Telithromycin				
		Macrocyclic		Fidaxomicin				
		Chloramphenicol		Chloramphenicol				
		Oxazolidinones		Linezolid	Tedizolid			
		Lincosamides		Clindamycin				
		Streptogramins		Quinupristin/Dalfopristin	Pristinamycin			
	Others			Fusidic Acid	Rifaximin	Retapamulin		
				Plazomicin	Mupirocin			
Nucleic Acid Synthesis	DNA Topoisomerases	Quinolones		Nalidixic acid	Cinoxacin			
		Fluoro quinolones	Second	Ciprofloxacin	Norfloxacin	Ofloxacin		
				Enoxacin	Lomefloxacin	Pefloxacin		
			Third	Levofloxacin	Sparfloxacin	Grepafloxacin		
			Fourth	Trovafloxacin	Moxifloxacin	Gatifloxacin		
				Gemifloxacin				
	Antifolates	Sulfonamides		Sulfamethoxazole	Sulfadiazine	Silver Sulfadiazine		
				Sulfadoxine	Mafenide	Sulfacetamide		
		DHFR inhibitor		Trimethoprim	Pyrimethamine			
		CO		Co-Trimoxazole	Sulfadoxine/Pyrimethamine			

Cell Wall Inhibitors

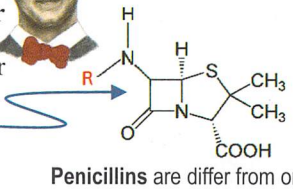
A) β-Lactam Antibiotics

I) Penicillins

➢ **Penicillins According to Spectrum of Activity :-** # #



- **Penicillins** *was* **discovered** in **1928** by *Scottish scientist* **Sir Alexander Fleming**.
- **Penicillin** *was* ***isolated*** ***naturally*** *from* ***Penicillium notatum*** (or ***Penicillium chrysogenum***).
- **Penicillins** are ***derivatives*** *of* **6-AminoPenicillanic Acid (6APA)**.
- ***Distribution***; **distribute** ***well*** *throughout the body*;
  - *Pass easily* **placental barrier** ☞ **Not Teratogenic**.
  - ***Not*** **penetrate CSF** ☞ **Pass** *easily* **in** ***inflamed*** **meninges**.
- ***Excretion***; ***Active*** **renal excretion** (***Inhibited by*** **Probenecid**).

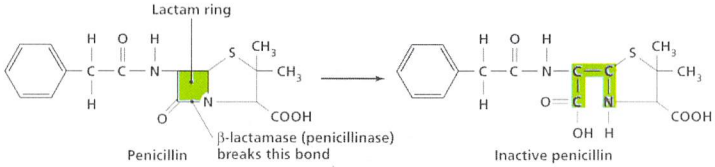


Penicillins are differ from one another in the **R** substituent attached to the **6APA** residue

Mechanism; **Penicillins** (and ***other*** **β-lactams**) *act by* ***binding with*** **Penicillin Binding Proteins (PBPs)** on **transpeptidase enzymes** ☞ ***Inactivation*** of **transpeptidase enzymes** which is *responsible for* ***formation*** of **peptide bond** (***cross-linkage***) during ***formation*** or ***repair*** of **peptidoglycan** ☞ ***Decrease*** **rigidity** of **cell wall** ☞ **cell wall** ***can't*** able to ***protect*** **bacterial cell** from ***high internal*** **osmotic pressure** ☞ ***cytolysis*** ☞ **death** (**Bactericidal**).

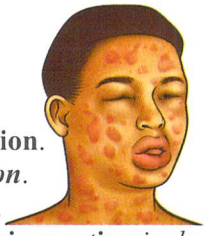
Bacterial Resistance;

1) **Enzymatic inactivation**; by **β-lactamase enzyme (Penicillinase)**.



2) ***Impermeability*** to **antibiotic** (*loss of* **Porin**). 3) **Efflux**.

4) ***Modification of target*** **Penicillin Binding Proteins (PBPs)**.



Most Common Adverse Reactions;

1) **Hypersensitivity Reactions; # # #**

- *About* **5%** of ***patients*** will ***develop*** a **hypersensitivity reaction**.
- **Hypersensitivity test** ***must be*** applied at **all time** of ***injection***.
- **Hypersensitivity test** may give ***false*** **negative result** (rare).
- **Anaphylactic shock** (***very rare***); is a ***life-threatening allergic reaction*** *include* those of an **allergic reaction**, as well as **bronchospasm** & ***severe*** **hypotension**.
  - ***Anaphylaxis Treatments***; ***Triple Therapy # #***

1) **Epinephrine**; **Physiologic Specific Antidote** [**Kiss of Life**];
   - **One** *ampoule* of **Epinephrine USP** = 1:1000 solution (1 mg in 1 mL).
   - If 1 ampoule is diluted to 10mL (Add 9ml of water for injection) = 1:10,000 (0.1 mg/1mL).
   - ***Dose*** **of Epinephrine in anaphylaxis**; ***Repeated*** every 5-10 min as necessary;
     - < 30 kg; **IM/SC** 0.1-0.3 mg (0.1 to 0.3 mL of 1:1000 OR 1 to 3 mL of 1:10,000).
     - ≥ 30 kg; **IM/SC** 0.3-0.5 mg (0.3 to 0.5 mL of 1:1000 OR 3 to 5 mL of 1:10,000).
2) **Solu-Cortef®** (**Hydrocortisone**); ***faster*** **corticosteroid**.
3) **Antihistamine** ***injection*** (**Avil®**).

Cross-allergic reactions *occur among* the **β-lactam antibiotics # #**

2) **Super-infection**; (Kill good bacteria in mouth and colon) # # #

- **Diarrhea☞ Pseudomembranous colitis** (***Clostridium difficile***); ***Treated by*** (***orally*** **Vancomycin#** # or **Metronidazole#**)
- **Candidiasis** (oral and/or vaginal); ***Treated by*** **Nystatin#** or **Miconazole#**.

Narrow Spectrum Penicillins

Ultra-short Acting

Penicillin G (Benzyl-penicillin)

- **Penicillin G** is ***not effective*** **orally** (destroyed by gastric acidity), it is ***administrated*** **IV** or **IM** (**IV** is ***preferred*** because of irritation and local pain from IM injection of large doses),
- **Penicillin G** has ***ultra-short*** **duration of action** (half-life; about 30 minutes).

2 long acting *forms* of **Penicillin G** are *available* for **IM injection**; **Benzathine benzylpenicillin** and **procaine benzylpenicillin**.

Uses and ***spectrum***;

- **Penicillin** ***remains*** the ***drug of choice***; **Gas Gangrene** (*Clostridium perfringens*), **Syphilis** (*Treponema pallidum*) and **Meningitis** (*Neisseria meningitidis*, *Streptococcus pneumoniae* and *Haemophilus influenzae*).
- **Bacterial Endocarditis** (*Staphylococcus aureus*, *Streptococcus viridans* and *Enterococci*)
- **Cellulitis** (*Streptococcus* and *Staphylococcus aureus*) and **Erysipelas** (*Streptococcus*).
- **Diphtheria** (*Corynebacterium diphtheriae*) and **Anthrax** (*Bacillus anthracis*).
- **Actinomycosis** (*Actinomyces israelii*) (painful abscesses in the mouth, lungs, breast, or GIT).
- **Tetanus** (*Clostridium tetani*); Combined with anti-toxins.

Short Acting

Penicillin V (Phenoxy-methyl-penicillin) (Ospen®)#

- **Penicillin V**, the ***oral form*** of **penicillin** (**Orally Penicillin**); ***more acid stable*** *than* **Penicillin G**.

Uses and ***spectrum***; **Penicillin V** has a ***similar spectrum*** to that of **Penicillin G**, ***but*** is ***indicate only*** in **minor infections** ***because*** of its *relatively* ***poor*** **bioavailability** (***not used*** for **bacteremia**).

- ***Dose***; - ***Adult***; 125-500 mg every 6-8 hours.
  - ***Children***; **< 12 years**; 25-50 mg/kg/day in *divided doses* every 6-8 hours.

Antibiotic Dose Calculation in Children

A) Child Weight Expectation;

- **Age**; 1-12 month; *Expected weight* (kg) = (age in months + 9)/2
- **Age**; 1-12 years; *Expected weight* (kg) = (age in years X 2) + 8
- *For Example* Child Weight = 20 Kg

B) Dose of the drug;

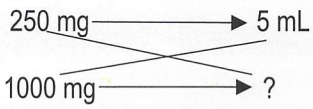
- *For Example* **Penicillin V**; 25-50 mg/kg/day in *divided doses* every 6-8 hrs.

C) Drug Concentration;

- *For Example* **Penicillin V**; 250mg/5mL

** Calculation **

- **Total Daily Dose**: 50 mg X 20 Kg = 1000 mg.



- **Total Daily Dose**: 1000 mg = 20 mL in divided doses every 6 hours = 5 mL every 6 hours.

Intermediate Acting

Procaine Penicillin (Procaine Benzylpenicillin) or Penicillin G Procaine

- **Procaine** (***local anaesthetic***) makes the **Benzylpenicillin** ***intermediate acting***, ***following*** deep **IM injection**, it is ***slowly absorbed*** into the **circulation** and ***hydrolysed to*** **Benzylpenicillin**, can ***last*** for ***up to*** **24 hours**.

Long Acting

Benzathine Penicillin (Benzathine Benzylpenicillin)

(Retarpen®)# (Durapen®) (Depo-Pen®) (Pencitard®)

- **Benzathine Penicillin** can ***last*** for ***up to*** **3-4 weeks** ***after*** a ***single*** **IM dose**.
- ***Dose***; - ***Adult***; 1.2-2.4 million unit IM as a *single dose*, in *secondary prevention every* 3-4 weeks or 600,000 units IM *every* 2 weeks.
  - ***Pediatric***; 50,000 units/kg/day IM as a *single dose* (*maximum*: 2.4 million units).

Indications; **Upper Respiratory Tract Infections**, **Rheumatic Fever** ***Prophylaxis***, **Skin or Soft Tissue Infection** (such as Cellulitis or Erysipelas) & **Syphilis** #.

Penicillinase-Resistant (Antistaphylococcal) Penicillins

Methicillin | **Oxacillin** | **Cloxacillin** | **Dicloxacillin** | **Flucloxacillin**

Antistaphylococcal penicillins are ***semisynthetic*** **penicillins** with **β-lactamase (penicillinase)-resistant**; their use is ***restricted*** to the **treatment** *of* ***infections*** caused by **Methicillin Sensitive *Staphylococcus aureus* (MSSA)**.

In ***recent years*** the **empirical use** of these drugs has ***decreased*** *substantially* ***because*** of ***increasing*** **rates** of **Methicillin-Resistance *Staphylococcus aureus* (MRSA)**.

MRSA is ***currently*** a ***source of*** **serious infections** and is ***resistant*** to ***most commercially*** *available* **β-lactam antibiotics**.

- **Methicillin** is ***not*** **absorbed** ***orally***, ***only*** **given** by **IV route** and has a ***higher*** **frequency** of **interstitial nephritis**.
- **Nafcillin** has ***poor*** **oral absorption** and is **given** by **IV** or **IM routes**, it is ***used for staphylococcal*** **endocarditis**.
- **Oxacillin**, **Cloxacillin**, **Dicloxacillin** and **Flucloxacillin** can be ***administered*** **orally**.
- ***Common combinations with*** **Aminopenicillins**;
  - **Cloxacillin** 250 mg + **Ampicillin** 250 mg; **Ampiclox®** 500 mg
  - **Dicloxacillin** 250 mg + **Ampicillin** 250 mg; **Cloxapen®** 500 mg
  - **Flucloxacillin** 125/250/500 mg + **Amoxicillin** 125/250/500 mg; **Flumox®** 250/500/1000 mg

Aminopenicillins

Ampicillin # | **Amoxicillin #**

- ***Unlike*** the ***natural*** **penicillins**, ***these agents*** exhibit ***increased*** **stability** in **gastric acid**.

Ampicillin and **Amoxicillin** have an **antibacterial spectrum** ***similar*** to that of **Penicillin G** but are ***more effective*** *against* **Gram -ve bacilli** (↑ penetrate the gm -ve outer membrane).

Bioavailability of **Amoxicillin** is ***greater than*** **Ampicillin** (***oral*** **Ampicillin** has been ***favored for*** treatment of a localized ***Shigella*** infection).

Absorption of **Ampicillin** is ***impaired*** by **food**, and the drugs ***should be*** administered ***at least*** **1 hour** ***before*** or **2 hours** ***after*** a **meal**.

- **Bacampicillin** is a ***prodrug*** of **Ampicillin** to ***increase*** **absorption**.
- **Ampicillin** (***with*** or ***without*** **Gentamicin**); ***drug of choice*** for ***Listeria monocytogenes***.

Ampicillin and **Amoxicillin** are ***excreted*** **unchanged** in the **urine**.

Doses; - ***Adult***; **250-500 mg** ***orally*** (**Ampicillin** ***every*** **6 hours** - **Amoxicillin** ***every*** **8 hrs**).
- **Ampicillin**; **500 mg** to **2 g IM/IV** ***every*** **6 hours**.
- ***Pediatric***; **25-50 mg/kg/day**; **Amoxicillin** **3** ***divided*** **doses**, **Ampicillin** **4** ***divided*** **doses**.

Most common side effects; **Diarrhea☞ Pseudomembranous colitis**.

Broad Spectrum Penicillins (Aminopenicillins + β-lactamase Enzyme Inhibitors)

Ampicillin/Sulbactam (Unasyn®)# | **Sultamicillin** (Unasyn® Oral)#

Co-Amoxiclav (Amoxicillin/Clavulanate) (Augmentin®)#

- **Sulbactam**, **Clavulanate** (**Clavulanic acid**), **Tazobactam** and **Avibactam** are **β-lactamase enzyme *inhibitors*** that are ***similar*** in **chemical structure** to **β-lactam antibiotics** *allows* to ***interact with*** the **β-lactamase enzyme** & ***irreversible inhibits*** **β-lactamase enzyme**.

Sultamicillin; is a ***prodrug*** ***oral*** ***form*** of the **Ampicillin/Sulbactam** ***results in*** **2.5 times** ***greater concentration*** of **Ampicillin** and **Sulbactam** ***than*** when ***given*** **alone**.

Indications; **Otitis Media, Sinusitis, Respiratory Tract Infections, Skin *and* Skin Structure Infections** and **Urinary Tract Infections**.

A) Amoxicillin/Clavulanate; (**Augmentin®**) (**Curam®**) (**Hibiotic®**) > > > ;

- ***Adult***; **500 mg** (**Augmentin® 625**) ***orally*** *every* **8 hours**
  OR; **875 mg** (**Augmentin® 1 gm**) ***orally*** *every* **12 hours**.
- ***Children*** **< 40 kg**; **20-45 mg/kg/day** ***divided doses every*** **8** or **12 hours**.

Augmentin® Family

- **Amoxicillin/Clavulanate** (4/1) dosed every **8 hours**;
  - **Augmentin®** Susp. 156mg/5ml
  - **Augmentin®** Susp. 312mg/5ml
- **Amoxicillin/Clavulanate** (7/1) dosed every **12 hours**;
  - **Augmentin®** Susp. 228.5mg/5ml
  - **Augmentin®** Susp. 457mg/5ml
- **Amoxicillin/Clavulanate** (14/1) dosed every 12 hrs [**Augmentin® High Dose** = 90mg/kg];
  - **Augmentin® ES-600**; **600 mg Amoxicillin /42.9 Clavulanic acid** in ***5 mL***;
    - **90 mg/kg/day** for **10 days** in ***recurrent*** or ***persistent acute*** **otitis media**.
- **Amoxicillin/ 125 mg Clavulanate Tablets**;
  - **Augmentin®** Tab. 375 mg; dosed *every* **8/12 hours**.
  - **Augmentin®** Tab. 625 mg; dosed *every* **8/12 hours**.
  - **Augmentin®** Tab. 1000 mg; dosed *every* **12 hours**.
- **Amoxicillin/Clavulanate Vials**;
  - **Augmentin®** Vial 600
  - **Augmentin®** Vial 1200
- **Others**;
  - **Augmentin® XR**; **1000 mg Amoxicillin /62.5 Clavulanic acid** in **1** ***tablet***;
    - **≥ 16 years**; **2 tabs** ***every*** **12 hrs** in **community acquired pneumonia**, **acute exacerbations** of **chronic bronchitis** & **acute bacterial sinusitis**; 7-10 days
  - **Augmentin®** Powder 1000 mg for adult have difficulty to swallow.
  - **Augmentin®** Infant Drops 6.25mg.

B) Ampicillin/Sulbactam (**Unasyn® - Unictam®**); **250, 375, 750, 1000, 3000 mg**;

- ***Adult***; **1.5-3 g IV** or **IM** ***every*** **6 hours** (**Sulbactam** ***not exceed*** **4 g** *per* **day**).
- ***Children*** **< 40 kg**; **300 mg/kg/day** ***divided doses every*** **6 hours** (**300 mg** ***represents*** the ***total*** **Ampicillin + Sulbactam**).

After reconstitution; use ***within*** **2 hours** if ***stored*** at **room temperature**, or *within* **4 hours** if ***stored*** *under* **refrigeration**.

C) Sultamicillin (**Unasyn® - Unictam®**); ***Adults***; is **375-750 mg** ***orally*** **twice daily**.

Anti-Pseudomonal Penicillins

Piperacillin (Pipracil®)	**Piperacillin/Tazobactam** (Tazocin®)# (Pipraztaz®)#

Developed to further increase *activity* ***against*** **Gm -ve resistant aerobes**, *especially* ***Pseudomonas aeruginosa*** ## and have **good** *activity* ***against*** **penicillinase-producing organisms** (for example, most ***Enterobacteriaceae*** and ***Bacteroides*** **species**).

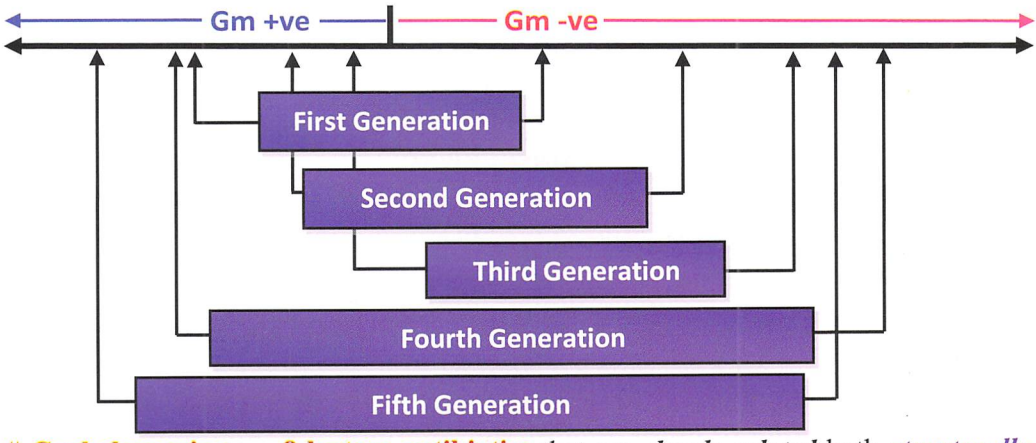
Doses;

Piperacillin + Tazobactam (**Tazocin®**) (**Pipraztaz®**);

- ***Adult***; **3.375 g IV** ***every*** **4-6 hours**.
- ***Children*** **< 40 kg**; **80-100 mg/kg IV** ***every*** **4-6 hours**.

II) Cephalosporins

➢ Cephalosporins According to Spectrum of Activity :- #



Cephalosporins are **β-lactam antibiotics** that are ***closely related*** both ***structurally*** and ***functionally*** to the **Penicillins**; have the ***same*** **mode of action** as **Penicillins**, and they are affected by the ***same*** **resistance mechanisms**.

- **Cephalosporins** ***was isolated naturally*** *from* ***Cephalosporium acremonium*** in **1945**.
- **Cephalosporins** are ***derivatives*** *of* **7-Amino-Cephalosporanic Acid (7-ACA)**.

Common Side effect of **Cephalosporins**;

Allergic reactions (**cross-sensitivity**);

- *About* **1%** of *patients* with a *history of* **Penicillin *allergy*** will have an ***allergic reaction*** if given a **Cephalosporin** (***especially*** **first-generation cephalosporins**).

Mild **stomach cramps** or **upset nausea**, **vomiting** and **diarrhea**.

Superinfection (***as*** **Penicillins**). - **Interstitial Nephritis**.

First Generation Cephalosporins		
Cefadroxil (Biodroxil®)# (Ibidroxil®)# (Duricef®)# (Curisafe®)# (Longicef®)		
Cephalexin (Ceporex®)# (Keflex®)# (Cephalex®)		
Cephradine (Velosef®)# (Cefadrin®)	**Cefazolin** (Zinol®)#	
Good **activity** ***against*** **Gram +ve**	***Staphylococcus*** spp. ***Streptococcus*** spp. ***Anaerobic streptococci***	★★
Some **activity** ***against*** **Gram -ve**	***Escherichia coli*** ***Klebsiella pneumoniae*** ***Proteus mirabilis***	★

Cefazolin is ***available only*** in ***parenteral*** **formulation** & it ***widely*** **used** ***peri-operatively*** to ***prevent*** **infections** ***post-surgery*** (***preferred drug*** for **surgical prophylaxis**).

This group *not* cross the **blood-brain barrier (BBB)** ⇨ ***Not effective*** in **Meningitis**.

Agent	Usual Adult Dose	Usual Children Dose
Cefadroxil	500-1000 mg orally every 12 hours	30 mg/kg/day orally divided every 12 hours
Cephalexin	250-500 mg orally every 6 hours	25-50 mg/kg/day divided every 6-12 hours
Cephradine	500-1000 mg orally every 12 hours	
Cefazolin	500-1000 mg IV every 6-8 hours	25-100 mg/kg/day IV/IM divided every 6-8 hrs

Second Generation Cephalosporins

Cefaclor (Ceclor®)# (Bacticlor®) (Cefaclor®) (Tabiclor®)

Cefuroxime (Zinnat®)# (Zinacef®) (Zenax®)

Cefprozil (Cefzil®)# | **Cefoxitin** (Orfixitin®)# (Primafoxin®)

Some **activity** *against* **Gram +ve**	***Staphylococcus aureus*** ***Streptococcus pyogenes*** ***Streptococcus pneumoniae*** **Anaerobic streptococci**	★
Good **activity** *against* **Gram -ve**	**Same as 1st generation** ***Haemophilus influenza*** ***Enterobacter aerogenes*** ***Neisseria*** spp.	★★

This group *not* cross the **BBB *except* Cefuroxime** (***less effective*** *than* **Ceftriaxone** or **Cefotaxime**).

Orally* Cefuroxime** is ***not* acceptable taste *need to* shaking** for **long time** to ↓ ***taste.

Cefotetan, **Cefoxitin** and **Cefmetazole** are ***only* second generation cephalosporins** have ***moderate*** **activity** *against* **anaerobes**.

Agent	Usual Adult Dose	Usual Children Dose
Cefaclor	250-500 mg orally every 8 hours	20-40 mg/kg/day orally divided every 8 hours
Cefuroxime	250-500mg orally every 12 hours 500-750 mg IV every 8 hours	30 mg/kg/day orally divided every 12 hours 75-150 mg/kg/day IV/IM divided every 8 hours
Cefprozil	250-500 mg orally every 12 hours	15-30 mg/kg/day divided every 12 hours
Cefoxitin	1-2 g IV every 6-8 hours	80-160 mg/kg/day IV divided every 4-6 hours

Third Generation Cephalosporins

Parenteral

Ceftriaxone (Rocephin®)# (Ceftriaxone®)# (Wintriaxone®)# (Triaxone®)# (Epicephin®)# (Cefaxone®)# (Oframax®) (Xoraxon®) (Cefotrix®) (Enoxirt®) >>>

Cefotaxime (Claforan®)# (Cefotax®)# (Rametax®) (Xorin®) (Foxime®)

Cefoperazone (Cefobid®)# (Cefazone®) | **Ceftazidime** (Fortum®)# (Cefidime®)

Oral

Cefixime (Ximacef®)# (Suprax®)# | **Cefdinir** (Omnicef®)# (Cefdin®) (Dinar®)

Cefpodoxime (Orelox®)# (Cefodox®) (Cefoprox®) | **Cefditoren** (Meiact®)#

Less **activity** *against* **Gram +ve**	***Streptococcus pneumoniae*** ***Streptococcus pyogenes*** **Anaerobic streptococci**	
Excellent **activity** *against* **Gram -ve**	**Same as 2nd generation** ***Pseudomonas aeruginosa*** ***Serratia marcescens***	★★★

Able to ***cross*** the **BBB**.

Broad spectrum of ***activity*** and ***further*** *increased* **activity *against* gram -ve**.

Ceftazidime & **Cefoperazone** are the ***only*** **2 drugs** ***have*** **antipseudomonal activity**.
Ceftazidime/Avibactam (**Avycaz**®); It was ***approved*** in **2015** for ***complicated*** **Intra-Abdominal Infections** (**cIAIs**) and ***complicated*** **Urinary Tract Infections** (**cUTIs**).
Cefoperazone 1000 mg in ***combination with*** **Sulbactam 500 mg** → **Sulperazon**®
Cefoperazone may ***cause*** **testicular atrophy** in **animals**, ***not*** **widely** ***used*** in **children**.
Ceftriaxone are **soluble** in **Lidocaine** and ***available*** in **IM** ***parenteral*** **formulations** (**IM ONLY**; to ***avoid*** **systemic toxicity** of **Lidocaine**).
DON'T MIX Ceftriaxone with a **Calcium-containing product** (**Ringer's solution**).
Ceftriaxone NOT used in **premature neonates** and **hyperbilirubinemic neonates**; ***displace*** **Bilirubin**.
The ***excretion*** of **Cefoperazone** and **Ceftriaxone** is ***mainly*** through the **biliary** tract, and **NO** ***dosage*** **adjustment** is ***required*** in **renal insufficiency**.
Common indications; **Otitis Media, Skin and Skin Structure Infections, Pharyngitis, Tonsillitis, Respiratory Tract Infections, Urinary Tract Infections, Bacterial Septicemia, Bone and Joint Infections, Intra-abdominal Infections** and **Surgical Prophylaxis**.

Agent	Usual Adult Dose	Usual Children Dose
Ceftriaxone	1-2 g/day IV/IM in single daily dose OR divided every 12 hours	50-75 mg/kg IV/IM in single daily dose OR divided every 12 hours
Cefotaxime	1-2 g IV every 8-12 hours	50-200 mg/kg/day IV/IM divided every 8-12h
Cefoperazone	2-4 g/day IV/IM divided every 12 h	100-150mg/kg/day IV/IM divided every 8-12h
Ceftazidime	500 mg-2 g IV/IM every 8-12 hours	30-50 mg/kg IV every 8-12 hours
Cefixime	400 mg/day orally in single daily dose OR divided every 12 hours	8 mg/kg/day orally in single daily dose OR divided every 12 hours (weight X 0.4 = mL)
Cefdinir	600 mg/day orally in single daily dose OR divided every 12 hours	14 mg/kg/day orally in single daily dose OR divided every 12 hours
Cefpodoxime	100-400 mg orally every 12 hours	5 mg/kg (max. 200 mg) orally every 12 hours
Cefditoren	*Approved only* for; ≥ 12 years; 200-400 mg orally every 12 hours	

Fourth Generation Cephalosporins

Cefepime (Maxipime®)# (Forcetex®)# (Wincef®)# | **Cefpirome** (Cefpirome®)#

- **This group** ***have*** an ***excellent*** **activity** ***against*** **Gram -ve** and **Gram +ve**.
- **This group** ***have*** **good activity** ***against*** ***Pseudomonas aeruginosa***, ***Staphylococcus aureus***, and ***multiple drug-resistant Streptococcus pneumoniae***.

- **Cefepime** (**Maxipime**®); ***used*** in;
  - **Pneumonia**.
  - ***Empiric*** **treatment of febrile neutropenic patients**.
  - ***uncomplicated*** **and** ***complicated*** **Urinary Tract Infections**.
  - ***uncomplicated*** **Skin** and **Skin Structure Infections** (**uSSSIs**).
  - ***complicated*** **Intra-abdominal Infections** (***in combination*** with **Metronidazole**).
  - **Brain abscess**.
- ***Doses***; **Cefepime**; - ***Adult***; 1-2 g IV every 8-12 hours. - ***Children***; 50 mg/kg IV every 12 hrs.
  Cefpirome; - ***Adult***; 1-4 g IV every 12 hours. - ***Children***; Not recommended.

- Febrile neutropenia is the development of fever, often with other signs of infection, in a patient with neutropenia.

III) Monobactams

Monobactams are β-lactam antibiotics wherein the β-lactam ring is alone (monocyclic β-lactam) and not fused to another ring, in contrast to most other β-lactams.

Aztreonam (Azactam®)#

Aztreonam, is the only commercially available monobactam.

Antimicrobial activity; primarily against Gram -ve, including Enterobacteriaceae and Pseudomonas aeruginosa (similar to 3rd generation cephalosporins).

It lacks activity against Gram +ve or anaerobes.

Administration; IV or IM and can accumulate in patients with renal dysfunction.

- It penetrates well into the cerebrospinal fluid.

Uses; Serious infections (pneumonia, meningitis, & sepsis) caused by susceptible Gm -ve in patients with hypersensitivity to penicillins (NO cross-hypersensitivity).

- Dose; - Adult; 1-2 g IV/IM every 8-12 hours.
  - Children; 30 mg/kg IV every 8 hours.

Nebulized forms of Aztreonam (Cayston®) is approved for cystic fibrosis.

IV) Carbapenems

Carbapenems are one of the MOST broad spectrum antibiotics

Carbapenems in general have seizure risk in high doses. → Nausea, Vomiting & Diarrhea

Most common side effects (more common with Imipenem); NVD, skin rashes and infusion reactions.

Renal failure; Doses must be adjusted (may lead to seizures); Meropenem, Doripenem, and Ertapenem are much less likely to cause seizures than Imipenem.

Imipenem/Cilastatin (Tienam®)#

- Imipenem is the first drug of this class, discovered by Merck in the mid-1970s.

Imipenem is compounded with Cilastatin [SYE-la-STAT-in] to protect it from metabolism by renal dehydropeptidase;

  # Imipenem is rapidly degraded by the Dehydropeptidase (Dipeptides) renal enzyme when administered alone (Nephrotoxic Metabolite).

  # Co-administered with Cilastatin (Dehydropeptidase enzyme inhibitors) ⇨ Prevent this inactivation (prevents formation of toxic metabolite and increase urinary concentration).

It is administered IV & penetrate well into body tissues fluids & CSF in inflamed meninges.

Spectrum of activity; aerobic, anaerobic, Gram +ve and Gram -ve including Pseudomonas.

Uses; Pneumonia, sepsis, endocarditis, joint infections, intra-abdominal infections and Urinary Tract Infections (UTIs).

Dose; - Adult (≥70 kg); IV; 250-1000 mg every 6-8 hours.

- Pediatric (for non-CNS infections); 25 mg/kg IV; every 12 hours in age less than 7 days.
  every 8 hours in age 1 to 4 weeks.
  every 6 hours in age 4 weeks to 3 months.
  15-25 mg/kg IV; every 6 hours in age 3 months or older.

Dose adjustment is needed in renal dysfunction

Meropenem (Meronem®)# (Mirage®) (Merostarkyl®) | **Ertapenem** (Invanz®)#

UN-LIKE Imipenem; **NOT** ***metabolized by*** **dehydropeptidase**.

LIKE Imipenem; **SAME** ***spectrum of*** **activity** (***Except*** **Ertapenem** is ***not*** **active** ***against***; ***Pseudomonas***, ***Acinetobacter*** and **enterococci**) #

Uses; - ***complicated*** **Skin and Skin Structure Infections (cSSSIs).**
- ***complicated*** **Intra-Abdominal Infections (cIAIs).**
- ***Community*****-Acquired Pneumonia (CAP).**
- **Febrile Neutropenia.**
- ***complicated*** **Urinary Tract Infections (cUTIs).**
- **Acute Pelvic Infections.**

Agent	Usual Adult Dose	Usual Children Dose
Meropenem	500-1000 mg IV *every* 8 hours	≥ 3 months; 10-40 mg/kg IV *every* 8 hours
Ertapenem	> 13 years; 1 g IV/IM *per* day	3 months-13 years; 15 mg/kg IV/IM *twice* daily.

B) Non-β-Lactam Antibiotics

Glycopeptide Antibiotics

Vancomycin

Vancomycin is ***active only*** ***against*** **Gram +ve**; **NOT effective** ***against*** **Gram -ve**; ***poorly*** **penetrate phospholipid membrane.** It is ***not absorbed*** after **oral** ***administration***.

FIRST-LINE;**1**) **IV Infusion**; ***complicated*** **skin infections, bacteraemia, endocarditis, bone** and **joint infections**, and **meningitis** ***caused by*** **Methicillin-resistant** ***Staphylococcus aureus*** (**MRSA**) & **Methicillin-resistant** ***Staphylococcus epidermidis*** (**MRSE**).

2) **Oral**; **Pseudomembranous colitis** ***caused by*** ***Clostridium difficile*** (**Oral capsules**; ***not absorbed*** & **Vancomycin** ***act*** **locally**).

Vancomycin ***inhibits*** **cell wall synthesis** by ***binding*** firmly to the **D-alanyl-D-alanine** (D-Ala-D-Ala) in ***peptidoglycan***, ***preventing*** *further* **elongation** of ***peptidoglycan***.

Vancomycin-resistant ***Staphylococcus aureus*** (**VRSA**); are a ***strains*** of **enterococci** ***resist*** **Vancomycin** by ***modification of*** the **D-Ala-D-Ala** ***binding*** **site**;

Dose; - **IV Infusion**; 15-20 mg/kg/*every* 8-12 hr (In a dilute solution #**slowly**#, over at least 60 min.).
- Dosage is reduced in patients with renal insufficiency.
- **Oral**; 125 mg orally *every* 6 hours for10 day {Powder for injection can be used to prepare oral capsules or solution for oral administration if not available or expensive}.
- **Inhalation** (*off-label*); via nebulizer; 250 mg (5 mL diluted vials) twice daily by nebulization.

Side Effects; # **Red Man Syndrome (RMS)** # # # or **Red Neck**; ***infusion reaction***

* ***Usually*** **appearing** ***rapidly*** *after* **infusion.**
* ***Non-specific*** **mast cell degranulation** → ↑ **Histamine** → ***Redness*** and ***hotness*** **in face and neck.**
* ***Treatments***; ↓ **infusion rate, use emollients, topical steroids, antihistamines** and **antibiotics.**
* ***Prophylaxis***; ***prolonging*** **infusion period to 1–2 hours** and ***pre-treatment*** **with antihistamine.**

Nephrotoxicity & **Ototoxicity**; ***increases*** the **toxicity** of ***other*** **nephrotoxins** or **ototoxins** such as **Aminoglycosides**. **Vancomycin** is **FDA** pregnancy ***category*** **B.**

Teicoplanin (Targocid®)#

Teicoplanin is a ***semi-synthetic derivative*** of **Vancomycin**, ***Unlike*** **Vancomycin**, it can be given **IM** or **IV** and has a ***long*** **half-life** (45–70 hrs); ***once-daily*** **dosing.**

Fosfomycin

Fosfomycin (Monuril®)#

Fosfomycin (**Phosphomycin** or **Phosphonomycin**) is a ***broad-spectrum antibiotic*** (***against many*** **Gram +ve** and **Gram -ve**), it is ***indicated*** in the ***treatment*** of **UTIs**.

Dose;

- ***Single*** **3 g dose** *for* ***uncomplicated*** **lower urinary tract infections**.
- **3 g** *every* **2** to **3 days** ***for*** **3 doses** *for* ***complicated*** **urinary tract infections** (*off-label*).
- **3 g** *every* **3 days** ***for*** **21 days** *for* **prostatitis** (*off-label*).

Pregnancy; ***FDA category*** **B**.

Polypeptide

Bacitracin

- **Bacitracin** is a ***cyclic peptide*** **mixture** (**polypeptide**) ***first*** obtained in **1943**.
- ***Spectrum***; ***active against*** **Gram +ve** **bacteria** (***high*** **molecular weight**; ***poorly*** **penetrate** **Gram -ve** ***phospholipid*** **membrane** and ***poorly*** **absorbed**).
- It is ***highly*** **nephrotoxic** when ***administered*** **systemically** and is **ONLY** ***used*** **topically**.
- It is often ***combined with*** **Polymyxin** or/and **Neomycin** (**Trivatracin®**); ***may cause*** **allergy** [Allergy due to Neomycin]

Cell Membrane Disruption Antibiotics

Polypeptide

Polymyxin B	Polymyxin E (Colistin)

Polymyxins ***inhibit many*** **important** **Gram -ve** **bacteria** including ***Pseudomonas aeruginosa***, ***Escherichia coli***, ***Klebsiella pneumoniae***, ***Acinetobacter*** **species** and ***Enterobacter*** **species**.

Polymyxins are ***relatively*** **neurotoxic** and **nephrotoxic**, so are usually ***used*** **ONLY** as a ***last*** resort in ***treating*** **infections** ***caused by*** **multiple drug-resistant** **bacteria**.

Only **2 forms** of **Polymyxins** are ***available*** in ***clinical used***;

- # **Polymyxin B**; *available as* **parenteral**, **ophthalmic** and **topical** ***preparations***.
- # **Polymyxin E** (**Colistin**); *available as* a **prodrug**, **Colistimethate sodium**, which is ***administered*** **IV** or **inhaled** via a **nebulizer**.

Lipopeptide

Daptomycin (Cubicin®)#

Daptomycin is a ***novel*** **cyclic lipopeptide**, ***used*** in the *treatment of* ***systemic*** and ***life-threatening*** **infections** caused by **Gram +ve** **bacteria**.

Spectrum; ***Similar to*** **Vancomycin**, ***but*** ***more rapidly*** **bactericidal** and ***active against*** **Vancomycin-resistant** ***strains*** of ***enterococci*** (**VRE**) & ***Streptococcus aureus*** (**VRSA**)

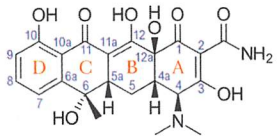
It is ***indicated for***; ***systemic*** and ***life-threatening*** **infections** *caused by* **Gram +ve**;

- ***complicated*** **Skin and Skin Structure Infections** (**cSSSIs**).
- ***Staphylococcus aureus*** **Bacteraemia**.
- ***Staphylococcus aureus*** **Endocarditis**.

- ***Dose***; 4-6 mg/kg IV *every* 24 hours.

Protein Synthesis Inhibitors

Tetracyclines



Low Lipid Solubility (Short-Acting)	High Lipid Solubility (Long-Acting)
Tetracycline (Sumycin®)	**Doxycycline** (Vibramycin®)# (Tabocin®)#
Oxytetracycline (Terramycin®)	**Minocycline** (Minocin®)
- ***Rarely*** **used** ***now***.	- ***Common*** **Tetracyclines used** ***now***.
- ***Affected*** by **food**; **chelation** ***with*** **metals** e.g. **Ca, Mg, Fe & Al** (tooth bleaching).	- ***Less*** **chelation**.
- **Fanconi Syndrome**;***nephrotoxic*** *metabolite*	- ***Not cause*** **tooth bleaching**.
	- ***Absence*** of **nephrotoxic** ***metabolite***.

Only **Doxycycline** and **Minocycline** ***achieve*** **therapeutic levels** in the **CSF**.

Minocycline *reaches* ***very high*** **concentrations** in **tears** and **saliva**, ***makes*** it **useful** for ***eradication of*** **meningococcal** ***carrier state***.

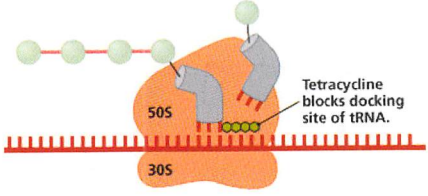
Tetracycline is ***eliminated*** **renally** and ***should not*** be **used** in **renal insufficiency**.

Doxycycline ***doesn't*** **need dose adjustment** in **renal** or **hepatic dysfunction**.

Mechanism; ***reversibly*** **bind** to **30S** ***subunit***, ***block*** **tRNA binding** **Bacteriostatic**.

High effective against (***Drug of choice***);

- **Rickettsia infection**.
- **Lyme disease**.
- **Mycoplasma pneumonia**.
- **Brucellosis**.
- **Chlamydial infections**.
- **Cholera**.



Also effective against;

- **Acne vulgaris**
- **Acne rosacea**.
- **Anthrax**.
- **Plague**.
- ***H. pylori***
- **Malaria & Filariasis**.
- **Syphilis** (*If* **Penicillin** is ***contraindicated***).

Doses;

Doxycycline; * **Oral** or **IV infusion**;

- **Adult**;
  - ***Initial***; *Oral*; 200 mg in 2 divided doses in the first day.
    IV Infusion; 200 mg in 1 or 2 divided doses in the first day.
  - ***Maintenance***; *Oral*; 100 mg orally once a day OR 50-100 mg orally every 12 hrs.
    IV Infusion; 100 to 200 mg/day IV infusion.
- **Children**;
  - ***Initial***; > 8 years; 4.4 mg/kg *orally*/*IV* on the first day, in 2 divided doses.
  - ***Maintenance***; > 8 years; 2.2 mg/kg *orally*/*IV* once a day OR 1.1 mg/kg twice

Minocycline; * **Oral** or **IV infusion**;

- **Adult**; 200 mg initially followed by 100 mg every 12 hours.
- **Children**; >8 yrs: 4 mg/kg initially followed by 2mg/kg/12hrs.

Side Effects;

GIT discomfort (*local irritation*); **Esophageal irritation**, **anorexia**, **NVD** (may be ***minimized*** by ***coadministration*** with **food** [***except*** **Tetracycline**] or **fluids** with ***standing up*** & ***use*** **capsule**.

Calcified tissues; **Discoloration** and **hypoplasia** of **teeth** and ***effect*** on **bone growth** in ***children less than*** **8 years** and **fetus** ***during*** **pregnancy** (**Teratogenic**; **Category D**).

Vestibular disturbance; **Dizziness**, **vertigo** & **tinnitus** ***particularly*** with **Minocycline**.

Photosensitivity; **Severe sunburn** ***may occur*** and ***more frequently*** with **Tetracycline**.

Hepatotoxicity; ***rare***, *but* **fatal**; may occur ***with*** **high IV doses**, ***particularly*** in **pregnancy** or **patients hepatic** or **renal** ***dysfunction***.

Renal Toxicity (***except*** **Doxycycline**); **Acidosis** and **azotaemia**.

Fanconi syndrome; Results by ***ingesting*** ***expired*** **Tetracyclines**; *converted to* **4-Epitetracycline** and **Anhydrotetracycline** which ***damage*** **proximal tubule**.

CONTRAINDICATIONS; **Children** ***less than*** **8 year** & **Pregnancy** (**Category D**)

PATIENT COUNSELLING # # # # # # #

1) ***Taken*** *with* **food** (***except*** **Tetracycline**), *with* ***large*** **amount** of **water** and ***remain*** **upright** *if possible*, and ***choose*** **capsule products**.
2) ***Don't take*** with **calcium-rich foods** as; **milk** & **milk products**.
3) ***Don't take*** with ***other drugs*** *specially*; **Ca**, **Iron** and **Antacids**.
4) ***Don't used*** for **children** ***less than*** **8 years** and **pregnancy**.
5) ***Avoid*** **sun exposure** **OR** ***Use*** **sun screen**.
6) ***Need*** **dose adjustment** in **kidney/liver failure** (***except*** **Doxycycline**).
7) **Check** ***for*** **expiry date**.

Glycylcyclines

Tigecycline (Tygacil®)#

- It is the ***first*** and ***only*** **glycylcycline**, ***more*** **effectively** ***than*** the **Tetracyclines**.

Spectrum; **Broad-spectrum activity** ***including*** those of **multi-drug resistance**; **MRSA**, **VRE**, **β-lactamase**–***producing*** **Gram -ve bacteria** and ***many*** **anaerobic**.
- ***Not*** **active against**; ***Proteus***, ***Providencia*** or ***Pseudomonas*** **species** (**PPP**).

Indications; - ***complicated*** **Skin and Skin Structure Infections** (**cSSSIs**).
- ***complicated*** **Intra-Abdominal Infections** (**cIAIs**).
- ***Community*-Acquired Pneumonia** (**CAP**).

- ***Dose***; - ***Adult***; > 17 years; 100 mg IV infusion *initial dose*, *followed by* 50 mg IV *every* 12 hours.
- ***Pediatric***; - 8 *to* 11 years; 1.2 mg/kg IV infusion *every* 12 hours.
- 12 *to* 17 years; 50 mg IV infusion *every* 12 hours.

Tigecycline ***primary*** **excreted** *via* **biliary/faecal** (***No*** **dose adjustments** in ***patients with*** **renal impairment**), ***However***, a ***dose reduction*** is ***recommended*** in ***severe*** **hepatic dysfunction**.

- ***Black box warning***; **Tigecycline** ***should be*** **reserved** ***for*** **use** in **situations** ***when*** **alternative treatments** are ***not*** **suitable**; ***increased*** **mortality**.
- **Tigecycline** may also ***have potential*** for **use** in **acute myeloid leukemia**.
- ***Side effects***; **LIKE Tetracyclines**.
- **Tigecycline** may ***decrease*** the **clearance** of **Warfarin** and ↑ **prothrombin time**.

Aminoglycosides

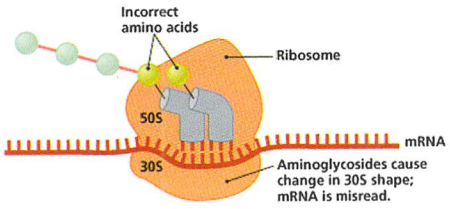
Streptomycin	Neomycin	Amikacin (Amikin®)#
Gentamicin (Garamycin®)#	Tobramycin (Tobrex®)#	

All **Aminoglycosides** (*except* **Neomycin**; *due to severe* **nephrotoxicity**) *must be* **given parenterally** (**IM** or **IV** *infusion*); ***absorbed*** *very* **poorly** *from* **GIT**.

Oral **Aminoglycosides** such as **Neomycin** can be ***used for*** **preoperative bowel preparation** and for **hepatic encephalopathy** or **hepatic coma** (act ***locally*** in ***ammonia-producing*** **bacteria**).

Once-daily dosing; *more* **effective**, *more* **convenient**, and *safer* **dosing regimen** ***than*** **2** or **3** ***equally divided*** **doses** but, ***generally*** *avoided* in ***patients with severe*** **renal impairment**.

Mechanism; **irreversibly bind** to the **30S subunit**, ***cause*** *misreading* of **mRNA**; **Bactericidal**.



Aminoglycosides are ***effective against*** **majority** of **aerobic Gram -ve bacilli** *including* those that may be ***multidrug resistant***, ***Pseudomonas aeruginosa***, ***Klebsiella pneumoniae*** & ***Enterobacter*** **spp.**

In *combination with* a **β-lactam** or **Glycopeptide** (**Vancomycin**): **Aminoglycosides** are ***effective against*** ***staphylococci*** (*including*; **MRSA**), ***streptococci*** and ***enterococci*** (***Enterococcal*** **endocarditis**) (**Gentamicin** and **Streptomycin** are the *best*); **β-lactams** and **Aminoglycosides** are ***administered*** in **2** **separate** **syringe** *due to* **acid/base** ***interaction***.

Gentamicin and **Streptomycin** is also ***useful against*** ***Francisella tularensis*** (**Tularemia**; is a **pneumonia** *acquired* during **rabbit hunting** season by ***hunters*** **skinning** ***infected*** **animals**), ***Yersinia pestis*** (**Plague**) and ***Mycobacterium*** (**Tuberculosis**).

Streptomycin (**Streptoquin®**) and **Neomycin** used in ***combination*** **or** ***alone*** with **antidiarrheal/antiseptic**; **locally** ***killing*** **bacteria** ***that cause*** **diarrhea**.

Side Effects; **OTOTOXICITY**, **NEPHROTOXICITY**, **Neuromuscular paralysis**.

- ***Risk*** of **nephrotoxicity** are ***increased by***; **Concurrent use** of **NSAIDs**, **Diuretics**, **Cisplatin**, **Cyclosporine**, **Cephalosporins**, **Amphotericin** and **Vancomycin**.

Agent	Usual Adult Dose	Usual Children Dose
Streptomycin	15-30 mg/kg/day OR 1-2 g IM only	20-40 mg/kg/day IM only
Gentamicin Tobramycin	*Conventional*; 1-2.5 mg/kg/dose IV/IM every 8-12 h *Once-Daily*; 4-7 mg/kg/dose IV once daily	≥ 5 years: 2-2.5 mg/kg/dose IV/IM every 8 hrs < 5 years: 2.5 mg/kg/dose IV/IM every 8 hrs
Amikacin	5-7.5 mg/kg/dose IV/IM every 8 hours (R; Lexicomp®)	
Neomycin	*Bowel Preparation*; 1 g orally every 1 hr for 4 doses *followed by* 1 g every 4 hrs for 5 doses *Hepatic Encephalopathy* (or *Coma*); 4-12 g/day orally divided every 4-6 hours for 5-6 days	*Bowel Preparation*; 90 mg/kg/day orally divided every 4 hours for 2-3 days *Hepatic Encephalopathy* (or *Coma*); 50-100 mg/kg/day orally divided every 6-8 hrs for 5-6 d

Macrolides

Erythromycin (Erythrocin®)#	**Clarithromycin** (Klacid®)# (Klacid® XL)#
Azithromycin (Zithromax®)# (Zisrocin®)# (Xithrone®)# (Azimak®)	
Spiramycin (Rovamycin®)# (Rovac®)#	
Roxithromycin (Roxicin®)	**Josamycin**

Erythromycin base is ***destroyed by*** **gastric acid** and ***must be*** **given** as *either* **enteric-coated** or ***more-stable*** **salts** or **esters**. **Clarithromycin** & **Azithromycin** are ***stable*** in **stomach acid**.

Food ***interferes*** with the **absorption** of **Erythromycin** and **Azithromycin** (**Azithromycin capsules** and **extended release suspension** ***should*** be ***administered*** **1 hour** ***before*** or **2 hours** ***after*** **meals**, ***while*** **Azithromycin tablets** and **immediate release suspension** can be ***taken with*** or ***without*** **food**). **Food** *slightly* ***delays*** the **onset** of **Clarithromycin absorption**, but ***increases*** the ***peak*** **plasma concentration** by *about* **24%**.

Azithromycin ***have*** *relatively* ***low*** **serum concentrations** and ***penetrates*** into **most tissues** (*except* **CSF**); with **tissue concentrations** ***exceeding*** **serum concentrations** by **10-100-fold** (**tissue** ***half-life*** of **2–4 days**) to ***produce*** an ***elimination*** **half-life** *approaching* **3 days** (***For example***, a ***single*** **1-g dose** of **Azithromycin** is ***as effective as*** a **7-day course** of **Doxycycline** for **chlamydial cervicitis** and **urethritis**).

Spiramycin ***crosses*** the **placenta** and ***reaches*** **concentrations** in the **placenta** ***up to*** **5 times** ***higher than*** **serum**; ***used*** to treat **toxoplasmosis** ***during*** **pregnancy**.

Erythromycin (***potent*** **liver microsomal enzyme inhibitor**; **CYP1A2, CYP3A4**) is ***extensively*** **metabolized** ***by*** **CYP450** ***system***; **Interference** with the ***metabolism*** of **drugs**, such as **Theophylline**, **Statins** and ***numerous*** **Antiepileptics**.

Clarithromycin is ***partially*** **metabolized** by **CYP3A4**.

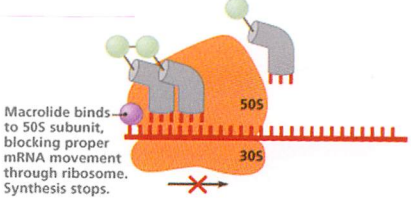
Azithromycin ***does not*** **inactivate** **CYP450 enzymes**; it has a **15-*member*** ***not*** **14-*member*** **lactone ring** like **Erythromycin** and **Clarithromycin**; ***not*** **CYP450 substrate**.

Erythromycin and **Azithromycin** are ***primarily*** **excreted** in the **bile** *via* **feces**.

Clarithromycin and ***its*** **metabolites** are ***eliminated by*** the **kidney**; **Dose** ***should be*** **adjusted** in ***patients with*** **renal impairment**.

Mechanism; ***irreversibly*** **bind** to **50S subunit**, ***inhibit*** **translocation**; **Bacteriostatic** in *general*.

Clarithromycin and **Erythromycin** are ***similar*** **antibacterial activity** *except* that **Clarithromycin** is ***more active against*** ***Mycobacterium avium*** **complex**, ***Chlamydia***, ***Legionella***, ***Moraxella***, ***Ureaplasma*** **species** & ***Helicobacter pylori***.



Clarithromycin also ***active against*** ***Mycobacterium***, ***Toxoplasma gondii*** and ***Haemophilus influenzae***.

Azithromycin is ***slightly*** ***less*** **active** than **Erythromycin** and **Clarithromycin** ***against*** ***streptococci*** and ***staphylococci*** and ***slightly*** **more active** ***against*** ***Haemophilus influenzae***.

Azithromycin is ***active against*** ***Mycobacterium avium*** **complex** (**MAC**) and ***Toxoplasma gondii***.

Azithromycin is ***highly*** ***active against*** ***Chlamydia*** **species**.

Indications;

Mycoplasma pneumoniae.

Pertussis (whooping cough) (***Bordetella pertussis***).

Otitis media, sinusitis & **bronchitis** (***Moraxella, S. pneumoniae*** & ***H. influenzae***)

Pharyngitis and **tonsillitis** (***Streptococcus pyogenes***).

Pyogenic skin infection (***Staph. aureus*** or ***Streptococcus pyogenes***).

Acne vulgaris (***Propionibacterium acnes***).

***Chlamydia* Infections**; **Azithromycin**.

***Campylobacter* gastroenteritis**; **Erythromycin - Azithromycin**.

Helicobacter pylori; **Clarithromycin**.

Diphtheria (***Corynebacterium diphtheriae***); **Erythromycin**.

Toxoplasmosis *during* Pregnancy (***Toxoplasma gondii***); **Spiramycin**.

Bacterial endocarditis (rheumatic fever) in **patients** who ***cannot*** take **Penicillins**.

Erythromycin is the ***most potent* prokinetic drug** *when given* **IV** and *may be* **used** to ***improve* delayed stomach emptying** in ***patients*** *with* **severe gastroparesis**.

Agent	Usual Adult Dose	Usual Children Dose
Erythromycin	250-500 mg (Base, Estolate, Stearate) OR 400 to 800 mg (Ethylsuccinate) orally *every* 6 hrs	40-50 mg/kg/day orally in divided doses *every* 6 hours.
Clarithromycin	*Immediate-release*; 250-500 mg orally every 12 hrs OR *Extended-release* (Klacid® XL); 1000 mg (two 500 mg extended release tablets) orally every 24 hours	7.5 mg/kg orally every 12 hrs
Spiramycin	**Mild-Moderate infections**; 6-9 million IU (4-6 cap. of 500mg)/day in 2 divided doses **Severe infections**; 12-15 million IU (8-10 cap. of 500 mg)/day in 2 divided doses **Gonorrhoea**: 12-13.5 million IU (8-9 capsules of 500 mg) as a single dose.	

Doses of **Azithromycin**;

Azithromycin capsules and **extended release suspension *should*** be ***administered* 1 hour *before*** or **2 hours *after* meals**, ***while* Azithromycin tablets** and **immediate release suspension** can be ***taken with*** or ***without* food**.

1 g *orally once* as a **single dose**; **Chancroid (genital ulcer disease)**, **gonococcal infection** {***gonorrhea***} (or; **2 g *orally* once**), **non-gonococcal urethritis** (*such as*; **chlamydia infection**) and **sexual transmitted disease *prophylaxis***.

Concn.	Dosage Form	Description	
250 mg	6 tab/cap	2 tab/cap once *daily* for *consecutive* 3 days/week OR 2 tab/cap once *in the* first day and 1 capsule in day 2 to day 5	
	4 tab/cap	4 tab/cap once; 1 g orally once as a single dose	
500 mg	3 tab/cap	1 tab/cap once *daily* for *consecutive* 3 days/week	
	5 tab/cap	1 tab/cap once *daily* for *consecutive* 5 days/week	
600 mg	3 tab/cap	1 tab/cap once *daily* for *consecutive* 3 days/week	
100mg/5mL 10 mg/kg	Suspension *Dose*; Weight/2= mL	15 mL	10 kg; 5 ml/day for *consecutive* 3 days/week
		22.5 mL	15 kg; 7.5 ml/day for *consecutive* 3 days/week
		30 mL	20 kg; 10 ml/day for *consecutive* 3 days/week
		60 mL	40 kg; 20 ml/day for *consecutive* 3 days/week
200mg/5mL 10 mg/kg (Zithromax®)	Suspension *Dose*; Weight/4= mL	15 mL (600 mg)	20 kg; 5 ml/day for *consecutive* 3 days/week
		22.5 mL (900 mg)	30 kg; 7.5 ml/day for *consecutive* 3 days/week
		30 mL (1200 mg)	40 kg; 10 ml/day for *consecutive* 3 days/week
2 g	Suspension (Zmax®)	Adult; ***Should be*** taken as a ***single*** 2 g dose Pediatric; ***Should be*** taken as a ***single*** dose of 60 mg/kg	
500 mg	Vial	Infusion rate; should be either 1 mg/mL over 3 hrs or 2 mg/mL over 1 hr	

Side Effects; # **GIT discomfort** (***especially*** with **Erythromycin** is a **prokinetic agent**).

Cholestatic hepatitis (***impaired* liver function**); *especially* **Erythromycin Estolate**.

QT interval *prolongation*; **Macrolides** may ***prolong* QT interval**.

Ototoxicity; ***especially* Erythromycin** at ***high dosages***.

Azithromycin *may cause* **taste/smell perversion *and/or* loss**.

Chloramphenicol

Chloramphenicol

- **Chloramphenicol** was ***isolated*** from the soil organism ***Streptomyces venezuelae*** in **1947**. ***Because*** of **potential toxicity**, ***bacterial* resistance**; **Chloramphenicol** is ***rarely* used** in the **United States** (**oral Chloramphenicol** in the **US *stopped*** in **1991**).
- **Chloramphenicol *binds reversibly*** to the **50S *subunit*** of the **bacterial ribosome** and ***inhibits* peptide bond *formation*** (***inhibit* peptidyl transferase**); **Bacteriostatic**.
- ***Formulations*** and ***uses***;
  - **Eye ointment** or **drops**; for **eye *infections***.
  - **Oral** (*was removed from the US market*).
  - **IV injection**; *only as* **alternative**.
    - **Typhoid Fever** (***3rd generation* Cephalosporins** & **Fluoroquinolones** are ***drug of choice***).
    - **Meningitis** (***3rd generation* Cephalosporins** are ***drug of choice***).
    - **Rickettsial Infection** (**Tetracyclines** are ***drug of choice***).

It is ***metabolized by*** the **liver** to **Chloramphenicol glucuronate** by **glucuronidation**.

Side Effects;

Bone marrow suppression; **rare**, **idiosyncratic reaction**; ***aplastic anemia***, ***thrombocytopenia*** and ***increased risk*** of **childhood leukemia**.

Hemolytic anemia; in **patients** *with* **glucose-6-phosphate dehydrogenase *deficiency***.

Gray baby syndrome; **Neonates** have a ***low capacity*** to **glucuronidation**, and they have ***underdeveloped* renal function**; which ***accumulates active* Chloramphenicol *levels*** that ***interfere with*** the **function** of **mitochondrial ribosomes**. This ***leads to*** *poor* **feeding**, ***depressed* breathing**, **cardiovascular collapse**, **cyanosis** (**gray baby**) and **death**.

- **Chloramphenicol** is a ***liver microsomal enzyme inhibitor***, thus ***decrease* metabolism** of ***other* drug** *such as*; **Antiepileptics** and **Anticoagulants**.

Oxazolidinones

Linezolid (Zyvox®)# (Averozolid®)# (Bactizolid®)# (Voxazoldin ®)# >>>

Linezolid is a ***synthetic* oxazolidinone *developed*** *to combat* ***resistant* Gram + ve *strains***, *such as*; - **Methicillin-resistant *Staphylococcus aureus*** (**MRSA**).
- **Vancomycin-resistant *Streptococcus aureus*** (**VRSA**).
- **Vancomycin-resistant *enterococci*** (**VRE**).
- **Penicillin-resistant *streptococci***.

***Advantage of* Linezolid *over* Tigecycline, Daptomycin** and **Vancomycin**;

Oral *formulation* is ***completely absorbed*** (**Bioavailability**: **100%**); **IV** is **available**.

Widely* distributed *throughout the **body**.

No* dose adjustments** are ***required for **renal** or **hepatic dysfunction**.

Used in **children** and **pregnancy** (***category* C**).

Local brands are ***less expensive***.

Indications; - ***Complicated* Skin & Skin Structure Infections (cSSSIs)**.
- ***Uncomplicated* Skin & Skin Structure Infections (uSSSIs)**.
- **Vancomycin-*Resistant Enterococcal* (VRE) Infections**.
- **Pneumonia**.

- ***Dose***;
  - ***Adult*** (≥12 years); 600 mg IV or oral *every* 12 hours; 10-14 (or 14-28 days *in VRE infections*).
  - ***Pediatric*** (<12 years); 10 mg/kg IV or oral *every* 8 hrs; 10-14 (or 14-28 days *in VRE infections*).

Side effects;

Most common; **GI upset, nausea, diarrhea, headache** and **rash**.

Hematologic (***reversible*** and *generally* **mild**); *due to* **bone marrow suppression** (*related to* **Linezolid**-*induced* ***inhibition*** of **mitochondrial protein *synthesis***);

- ***Most common***; **Thrombocytopenia** (*mainly* occur if ***used*** *longer than* **10 days**).
- **Anemia** and **neutropenia** *may also occur*.

Others;

SEROTONIN SYNDROME # # (**Linezolid** *possesses* ***non-selective*** **MAOI**).

Optic and **peripheral neuropathy** (**irreversible** and *mainly* occur if ***used*** *longer than* **28 days**) and **lactic acidosis** (*due to* **mitochondrial toxicity** and *mainly* occur if ***used*** *longer than* **several months**).

Drug interactions; **MAOIs** and ***other*** **Serotonergic Drugs**.

Monitoring;

Weekly **complete blood counts (CBC)** ***during*** **Linezolid therapy**.

Treatment last ***no more*** *than* **28 days**.

Tedizolid (Sivextro®) (Tedimerp®) (Zolidocyrl®)

Tedizolid is a ***second-generation*** **oxazolidinone** ***derivative*** that is **4-to-16-fold** ***more potent*** *against* ***staphylococci*** and ***enterococci*** compared to **Linezolid**.

Tedizolid has been ***approved by*** **US FDA** in **2014**, for the ***treatment*** of **Acute Bacterial Skin** and **Skin Structure Infections (ABSSSI)**.

Differences *between* **Linezolid** & **Tedizolid** are ***minor***; **dose interval** & ***duration*** **of therapy**.

- ***Dose***; **≥ 18 years**; **Oral** or **IV**: **200 mg** ***once daily*** for **6 days**.

Lincosamides

Clindamycin (Dalacin®-C)# (Clindam®)# >>

Clindamycin ***like*** **Erythromycin**; ***inhibits*** **protein synthesis** by ***inhibit*** **translocation**.

Resistance to **Clindamycin**, which *generally* ***confers*** **cross-resistance** to **Macrolides**.

It **used** ***primarily*** in ***many*** **Gram + ve anaerobes** & ***some*** of **Gram -ve anaerobes**.

High **concentrations** in **bone**, **teeth** & **urine** ***but poor*** **entry** into **CSF** *even* with ***inflamed***.

Preparations; **Capsules, Ampoules, Solution/Lotion/Gel/Foam** 1% & **Vaginal Cream/Suppository** 2% (Oral suspension is not favored; extremely foul taste and odour).

Indications; **Otitis media, sinusitis, bone** or **joint infections, dental infections, pelvic inflammatory disease, bacterial vaginosis, intra-abdominal anaerobic infections, pneumonia, endocarditis prophylaxis, bite wounds, inhalational/gastrointestinal anthrax, CNS toxoplasmosis, acne** and **malaria**.

Usual Adult dose; 150-300 mg orally *every* 6 hrs OR 600-1200 mg/day IV/IM divided *every* 12-6 hrs.

- ***Side effects***; **Diarrhea** (**pseudomembranous colitis**) **nausea** and **skin rashes**.

Others

Fusidic Acid (Fucidin®)#

Fusidic acid is a *steroid* antibiotic that *derived from* the fungus *Fusidium coccineum* and was *developed by* Leo Pharma and *released for* clinical use in the 1960s.

Fusidic acid is *often* used topically but *may* also be given *orally* or *parenterally*.

Spectrum; Primarily *against* Gram + ve; *such as* *Staphylococcus* species, *Streptococcus* species and *Corynebacterium* species.

Fusidic acid *should not* be used with Quinolones, with which they are *antagonistic*. When *combined* with Rifampicin, the action is *additive* or *synergistic*.

Systemic Fusidic acid *should not* be given with Statins *because* of a *risk* of *serious* and *potentially fatal* rhabdomyolysis.

Rifaximin (Gastrobiotic®)# (Trencedia®) (Trencedia®) (Idibact®) >>

Rifaximin is a *new* GI antibiotic, was *approved by* US FDA in 2004 *for* traveler's diarrhea, irritable bowel syndrome and hepatic encephalopathy; *poor* oral absorption (act *locally*).

Rifaximin may use *with* Vancomycin in *treating* patients *with* relapsing *Clostridium difficile*

Dose; - Traveler's Diarrhea; 200 mg orally *every* 8 hours for 3 days.
- Irritable Bowel Syndrome; 550 mg orally *every* 8 hours.
- Hepatic Encephalopathy; 550 mg orally *every* 12 hours.

Side effects; Flatulence, headache, abdominal pain, bowel urgency, nausea and rectal tenesmus (feeling of incomplete defecation).

Quinupristin/Dalfopristin (Synercid®)#

Quinupristin/Dalfopristin are *both* Streptogramin *antibiotics*, are *combined in* a weight-*to*-weight *ratio* of 30% Quinupristin to 70% Dalfopristin.

Spectrum; Primarily *against* Gram + ve *cocci*, including those *resistant* to *other* antibiotics; *Enterococcus faecium* (*including* VRE *strains*, but *not active* *against* *Enterococcus faecalis*), *penicillin-resistant* strains of *Streptococcus pneumoniae*, Methicillin *susceptible* and *-resistant* strains of *staphylococci* (MSSA and MRSA); cSSSIs, bacteremia, infective endocarditis and intravascular catheter-associated bacteremia. *Dose*; IV; 7.5 mg/kg every 8-12 hours.

Precautions; Quinupristin/Dalfopristin *must* be *mixed* and *administered* *with* 5% Dextrose *in* water solutions *only* (*insoluble* and can *crystallize* in normal saline).

Side effects; Phlebitis (*ideally* *should be* administered via a central line), *high incidence* of myalgias, arthralgias and hyperbilirubinemia.

Retapamulin (Altabax®)# (Altargo®)#

Retapamulin is the *first* drug in the *new class* of Pleuromutilin antibiotics *developed* *by* GlaxoSmithKline, used *topically* for skin infections *such as* impetigo.

Mupirocin (Bactroban®)#

Mupirocin is *rapidly* inactivated *after* absorption, and systemic *levels* are *undetectable*, so it is used *only* as topical preparations (3 times daily).

Mupirocin is a protein synthesis inhibitor that is *useful* in impetigo & *other* Gram +ve *including* MRSA; *should not* be *applied for* *longer than* 10 days to *avoid* resistance.

Nucleic Acid Inhibitors

Quinolones and Fluoroquinolones

Classification According to Generation

First

Quinolones

Nalidixic acid
Cinoxacin

- First generation ⇨ Quinolones.
- Second, Third and Fourth ⇨ Fluoroquinolones.
- First generation less used today.
- Moderate activity against Gram - ve.
- Nalidixic acid is the first quinolone drug (was introduced in 1962) during the manufacture of Quinine.

Second

Fluoroquinolones

Ciprofloxacin
Norfloxacin
Ofloxacin
Enoxacin
Pefloxacin
Lomefloxacin

- Expanded activity against Gram - ve (including *Pseudomonas* species)
- Some activity against Gram + ve.
- Some activity against atypical bacteria such as Mycoplasma and Chlamydia.

Third

Levofloxacin
Sparfloxacin
Grepafloxacin

- Retain expanded Gram - ve activity
- Improve activity against gram +ve and atypical bacteria.

Fourth

Trovafloxacin
Moxifloxacin
Gatifloxacin
Gemifloxacin

- They are also called respiratory Fluoroquinolones.
- Improve activity against Gram +ve.
- Gains anaerobic coverage.

There is another classification (1997) includes only Trovafloxacin in fourth generation

Antifolates

A) Sulfonamides

B) Dihydrofolate Reductase (DHFR) inhibitor (**Trimethoprim** and **Pyrimethamine**)

First Generation	
Nalidixic acid (NegGram®)# (Nalidram®)#	
Second Generation	
Ciprofloxacin (Cipro®)# (Ciprofar®)# (Ciprobay®)# (Rancif®) (Serviflox®)	
Norfloxacin (Noroxin®)# (Noracin®)	**Ofloxacin** (Tarivid®)# (Kiroll®)
Enoxacin (Penetrex®)# (Enroxil®)	**Lomefloxacin** (Lomax®)# (Lomeflox®)
Third Generation	
Levofloxacin (Tavanic®)# (Tavacin®)# (Levoxin®)# >>>	
Sparfloxacin (Parox®) (Spara®) (Zagam®)	
Fourth Generation	
Moxifloxacin (Avalox®)# (Moxiflox®)	**Gatifloxacin** (Tequin®) (Floxin®)
Gemifloxacin (Flobiotic®)# (Factive®)# (Quinabiotic®)# (Gemique®)	

- *Over* **10,000 Fluoroquinolone analogs** have been **synthesized**, including ***several*** with *wide* **clinical applications**

Fluoroquinolones available for ***systemic*** **use** in the **US** include; **Ciprofloxacin**, **Levofloxacin**, **Ofloxacin**, **Gemifloxacin** and **Moxifloxacin**.

All **Fluoroquinolones** are ***rapidly*** **absorbed**; **bioavailability**; **80-95%**, **Norfloxacin**, **Gemifloxacin** and **Ciprofloxacin** are ***lower*** **bioavailability**; **Calcium**, **Iron**, **Zinc**, **Sucralfate** and **Antacids** ***reduce*** the **absorption**; ***oral*** **Fluoroquinolones** ***should be*** **taken 2 hours** ***before*** or **4 hours** ***after*** *any* **products** ***containing these*** **cations**.

Ophthalmic preparations; **Ciprofloxacin** (**Ciloxan**®), **Levofloxacin** (**Quixin**®), **Gatifloxacin** (**Zymar**®) & **Moxifloxacin** (**Vigamox**®); **IV** ***preparations*** of ***this drugs*** are also ***available***.

Concentrations of **Fluoroquinolones** are ***above*** *those* in **serum** in **bone**, **urine**, **kidney**, **prostatic** and **lungs**;

- ***Lowest*** **urine concentrations** are **Moxifloxacin** and **Gemifloxacin** (***not used*** in **UTIs**).
- ***Highest*** **urine concentrations** are **Gatifloxacin** and **Levofloxacin** (**excreted** by the **kidney** completely **unchanged**).

Ciprofloxacin and **Ofloxacin** have ***good penetration*** into **cerebrospinal fluid** (**CSF**) in **inflamed meninges**.

Most **Fluoroquinolones** are ***excreted*** **renally** (**dosage adjustments** are ***needed*** in **renal** ***dysfunction***); **Moxifloxacin** is ***excreted*** **primarily** by the **liver** (***no dose*** **adjustment** is ***required for*** **renal impairment**); **dosage adjustments** are ***needed*** in **liver** ***dysfunction***.

Levofloxacin, **Gemifloxacin**, **Gatifloxacin** and **Moxifloxacin** has ***relatively*** **long half-lives**, ***permit*** ***once***-**daily dosing**.

Mechanism; **Bactericidal**; **Fluoroquinolones** ***block*** **bacterial DNA** ***synthesis*** by ***inhibiting*** **bacterial Topoisomerase II** (**DNA Gyrase**) and **Topoisomerase IV**.

- ***Inhibition*** of **DNA Gyrase**; ***more significant*** in **Gram -ve**;
  - **Agents** with ***higher*** **affinity** for **Topoisomerase II** (*such as* **Ciprofloxacin*** and **Levofloxacin**) ***more potent*** **activity** ***against*** ***Pseudomonas aeruginosa***.
- ***Inhibition*** of **Topoisomerase IV**; ***more significant*** in **Gram +ve**.
  - **Agents** with ***higher*** **affinity** for **Topoisomerase IV** (*such as* **Moxifloxacin***, **Gemifloxacin** and **Gatifloxacin**) ***more potent*** **activity** against ***Streptococcus pneumoniae***.

Spectrum of activity;

- **Quinolones** such as **Nalidixic acid** did ***not achieve*** **systemic antibacterial** ***levels*** and were **useful** ***only*** in the **treatment** of ***lower*** **Urinary Tract Infections** (**UTIs**).
- **Fluorinated** ***derivatives*** (**Fluoroquinolones**) ***achieve*** **bactericidal** ***levels*** in **blood** and **tissues**.
- **Fluoroquinolones** were ***originally*** **developed** ***because excellent*** **activity** ***against*** **Gram -ve aerobic**; ***E. coli***, ***Pseudomonas aeruginosa***, ***Haemophilus influenzae***, ***Klebsiella pneumoniae***, ***Legionella pneumophila***, ***Proteus mirabilis***, ***Shigella*** and ***Enterobacter*** **spp**.
- ***Several*** **newer agents** have ***improved*** **activity** ***against*** **Gram +ve** ***cocci***.

- **Norfloxacin** is the ***least* active** of **Fluoroquinolones *against*** *both* **Gram -ve** and **Gram +ve**.
- **Ciprofloxacin**, **Enoxacin**, **Lomefloxacin**, **Ofloxacin**, **Levofloxacin** and **Pefloxacin** ***possessing excellent* Gm -ve *activity*** & ***moderate*** to ***good*** **activity *against* Gm +ve**.
- **Ciprofloxacin** (**THE BEST**) and **Levofloxacin** are ***most potent* activity *against* *Pseudomonas aeruginosa***.
- **Levofloxacin** has ***superior* activity *against* Gram +ve *organisms***, including ***Streptococcus pneumoniae***.
- **Moxifloxacin** (**THE BEST**), **Gatifloxacin** & **Gemifloxacin *improved* activity *against* Gram +ve *organisms*, *particularly* *Streptococcus pneumoniae*** and ***some staphylococci***.
- **Moxifloxacin** is the ***only approved*** has ***modest*** **activity *against* anaerobic *bacteria***.

Indications;

Ciprofloxacin (**Cipro**®), (**Ciprofar**®),(**Ciprobay**®), (**Rancif**®),(**Serviflox**®), >>>

* **Urinary Tract Infections**; *Adult and Children*
* ***Chronic* Bacterial Prostatitis**.
* **Urethral & Cervical Gonococcal Infections**.
* **Infectious Diarrhea**.
* **Anthrax & Plague** (*prophylaxis & ttt*); *Adult & Children*
* **Typhoid Fever**.
- **Intra-abdominal Infections**.
- **Bone & Joint Infections**.
- **Skin/Skin Structure Infections**.
- ***Acute* Sinusitis**.
- ***Lower* Respiratory Tract Infections**.
- ***Nosocomial* Pneumonia**.
- **Empirical Therapy** in **Febrile Neutropenic Patients**.
- ***Non-cystic* Fibrosis Bronchiectasis**; *Dry powder for inhalation.*

Levofloxacin (**Tavanic**®)# (**Tavacin**®)# (**Levoxin**®)# >>>

* ***Uncomplicated* & *Complicated* Urinary Tract Infections**.
* ***Chronic* Bacterial Prostatitis**
* **Anthrax & Plague** (*prophylaxis & ttt*); *Adult & Children*
* **Acute Pyelonephritis**.
- ***Acute* Bacterial Sinusitis & *Community*-Acquired Pneumonia**; *Adult (& Children off-label)*
- ***Acute* Bacterial Exacerbation** of **Chronic Bronchitis**.
- ***Nosocomial* Pneumonia**.
- **Skin/Skin Structure Infections**.
- **Epididymitis & Acne** (*Off-label*).
- ***Pseudomonas aeruginosa* Pulmonary Infections** (**Quinsair**®); Inhalation.

Moxifloxacin (**Avalox**®)# (**Moxiflox**®);

* ***Acute* Bacterial Sinusitis**. * ***Community*-Acquired Pneumonia**.
* ***Acute* Exacerbation** of **Chronic Bronchitis**. * **Skin & Skin Structure Infections**.
- **Intra-abdominal Infections**. - **Pneumonic & Septicemic Plague**.

- **Fluoroquinolones** has also ***activity against M. tuberculosis***.
- **Ofloxacin** and **Levofloxacin** are ***second line therapy*** for ***Chlamydia* Infection** *after* **Azithromycin 1 g *single dose*** or **Doxycycline 100 mg *twice*** daily *for* **7 days**.

- ***Doses***; **Ciprofloxacin** & **Levofloxacin** are ***available as*** **oral suspensions** in ***many*** **countries**.

Agent	Usual Adult Dose	Usual Children Dose
Ciprofloxacin	500-750 mg orally every 12 hours OR 400 mg IV every 12 hours	10 mg/kg orally or IV every 12 hours (Ciprofloxacin and Levofloxacin are the ***only*** Fluoroquinolones ***used*** in pediatrics and children)
Norfloxacin	400-800 mg orally every 12 hours	<18 years: Safety and efficacy not established
Ofloxacin	200-400 mg orally every 12 hours	<18 years: Safety and efficacy not established
Levofloxacin	500-750 mg orally/IV every 24 hrs	8 mg/kg orally/IV every 12 hours
Moxifloxacin	400 mg orally/IV every 24 hours	<18 years: Safety and efficacy not established
Gatifloxacin	200-400 mg orally/IV every 24 hrs	<18 years: Safety and efficacy not established
Gemifloxacin	320 mg orally every 24 hours	<18 years: Safety and efficacy not established

Side Effects;

In general; **Fluoroquinolones** are ***generally*** **well tolerated**. **Like** ***most*** **antibiotics**, ***most common*** **side effects** are **nausea**, **vomiting** and **diarrhea**.

CNS; - ***Common***; **Headache**, **dizziness** & **insomnia**.

- ***Less common***; **Hallucinations** & **depression**.

- ***Rare***; **Neurotoxicity** (**Seizures**) ***inhibit*** **GABA**; [*especially with* **Norfloxacin** and **Ciprofloxacin**]; ***Only*** in **patients** ***underlying*** **neurologic diseases** (**epilepsy**), ***renal*** **insufficiency** or ***concomitant*** **use** of **neurotoxic drug**.

Cardiovascular; **QT interval** ***prolongation*** [*especially with* **Levofloxacin**, **Gatifloxacin**, **Gemifloxacin** and **Moxifloxacin**].**Moxifloxacin** ***carries*** the ***greatest*** **risk**, *while* **Ciprofloxacin** ***appears to*** be ***associated with*** the ***lowest*** **risk**.

Dermatologic; **Photosensitivity**; ***Severe*** **sunburns** ***may occur***; can be ***avoided*** or ***prevented*** by ***avoiding*** *exposure* to **sunlight** or ***should be*** *advised to* ***use*** **sunscreen**.

Musculoskeletal; - **Articular Cartilage Erosion** (**Arthropathy**) has ***been observed***. ***Thus***, **these drugs** are ***not*** ***routinely*** *recommended for* **patients** ***under*** **18 years** *of* **age** (***Except***; **Ciprofloxacin** and **Levofloxacin** in ***some*** **indications**).

- **Tendon rupture**; a ***rare*** **complication** that has been ***reported in*** **elderly**, ***patients with*** **renal dysfunction** & ***those*** **taking Corticosteroids**

Glucose Metabolism; **Gatifloxacin** has been ***associated with*** **hyperglycemia** in **diabetic patients** and *with* **hypoglycemia** in **patients** also ***receiving*** **oral hypoglycemic** ***agents*** (*withdrawn in US in* 2006).

In 2016; **FDA** *required* the ***addition*** of a **warning** for all systemic **Fluoroquinolones** that *their* **risks** ***outweigh*** *their* **benefits** for ***most cases*** of **sinusitis**, **bronchitis**, and ***uncomplicated*** **UTIs** ***unless*** **other options** are ***not*** **available**.

In 12/2018; **FDA issued a warning about the risk of aortic aneurysm and dissection with Fluoroquinolones.**

 # # # # # # # # PATIENT COUNSELLING # # # # # # # #

1) ***Don't take*** with **calcium-rich foods** as; **milk** & **milk products**.
2) ***Don't take*** with ***other drugs*** *specially*; **Ca**, **Iron** and **Antacids**.
3) ***Don't take*** with **Corticosteroids** ***especially*** in **elderly** & **patients** *with* **renal dysfunction**
4) ***Don't used*** for **children** ***less than*** **18 years** and **pregnancy**.
5) ***Used cautiously*** in **epileptic patients**.
6) ***Avoid*** **sun exposure** **OR** ***Use*** **sun screen**.
7) ***Need*** **dose adjustment** in **kidney failure** (***except*** **Moxifloxacin**).

Antifolate Antibiotics

Co-Trimoxazole (Trimethoprim/Sulfamethoxazole) (Septrin-D.S.®)#

Combining the **Sulfonamide** (**Sulfamethoxazole**; **SMX**) with **Dihydrofolate Reductase** (**DHFR**) ***inhibitor*** (**Trimethoprim**; **TMP**); the **generic name** for the ***combination*** is **Cotrimoxazole**; ***provides*** a **synergistic combination**.

Cotrimoxazole OR **Sulfamethoxazole** (**SMX**)/**Trimethoprim** (**TMP**) is the ***most widely*** used **antifolate**; ***broad-spectrum*** **against** *both* **Gram +ve** & **Gram -ve** ***bacteria*** and ***some*** **protozoa**.

Mechanism; **Cotrimoxazole** ***blocks*** **2 consecutive** ***steps*** in the ***biosynthesis*** of **nucleic acids** in ***many*** **bacteria**.

1) ***Due to*** **structural similarity** *between* **Sulfonamides** &**P-Amino-benzoic acid** (**PABA**) ⇨ ***Compete*** with **PABA** ⇨ ***Inhibition of*** **Dihydropteroate synthase**.

2) **Trimethoprim** ***inhibits*** **Dihydrofolate reductase**.

* **From 1** and **2** ⇨ ***Inhibit of*** **Folic acid** ***synthesis*** which is ***essential for*** *synthesis of* **DNA**.

Advantage of combination (**SMX/TMP**);

- **Synergistic effect**.
- ***Decrease*** the **bacterial resistance**.
- **Bactericidal action**.
- ***Decrease*** the **dose** of **each one**.
- ***Increase*** the **spectrum of activity**.

Spectrum of activity; ***Staphylococcus aureus*** (*including* many **MRSA strains**), ***Streptococcus pneumoniae***, ***Streptococcus pyogenes*** ***Haemophilus influenzae***, ***Escherichia coli***, ***Salmonella***, ***Shigella***, ***Klebsiella pneumoniae***, ***Nocardia***, ***Stenotrophomonas maltophilia***, ***Listeria monocytogenes*** & ***Pneumocystis jirovecii***.

Indications; **Urinary tract infections**, **respiratory tract infections** and **gastrointestinal tract infections** & ***other*** **infections** caused by ***sensitive*** **organisms**.

Dose; **TMP/SMX** *comes* in a ***fixed*** **1:5 ratio** of the ***two*** **components**.

- **Tablets**; - ***Single*-Strength**; **Septrin®** (80:400 mg **TMP**:**SMX**).
  - ***Double*-Strength**; **Septrin-D.S.®** (160:800 mg **TMP**:**SMX**); 1-2 tab. orally every 12-24hr.
- **Oral Suspension**; **>2 months**; 8-10 mg **TMP**/kg/day PO divided every 12hr.
- **IV**; 8-20 mg **TMP**/kg/day IV *every* 6-12hr.

Side Effects;

Dermatologic: - **Rash** (***much*** **more common** in **AIDS patients** and ***severe*** in **elderly**).
- **Stevens-Johnson syndrome** *also occur* *but* **rare**.

GIT; **Nausea**, **vomiting** and **diarrhea**.

Hematologic; - **Bone-marrow suppression** (dose-dependent).
- **Hemolytic anemia**; *may occur* in **patients** *with* **G6PD** ***deficiency***.

Renal; **Crystalluria** (blood urea and creatinine elevations), **acute interstitial nephritis** and can ***lead to*** **acute renal failure** (*very rare*).

Electrolytes; **Hyperkalemia**.

Newborns; **Kernicterus** (Bilirubin-induced brain dysfunction; Neurotoxic hyperbilirubinemia).

Contraindications; **hypersensitivity** to **sulfa**, **Age <2 months**, **CrCl <15 mL/min**, **G6PD deficiency** (**Favism**), **hepatic impairment**, **pregnancy** & **nursing mothers**.

Drug interactions; ***Increase*** **concentration** of **Phenytoin** & **Warfarin** (inhibit metabolism) and **Methotrexate** (displacement from plasma proteins).

N.B.; **Trimethoprim** is ***about*** **50,000 times** ***less efficient*** in ***inhibition*** of **mammalian Dihydrofolic acid reductase**. **Trimethoprim** is **20-** to **50-fold** ***more*** **potent** ***than*** the **Sulfonamides**.

Sulfadiazine/Pyrimethamine is used ***for*** **Toxoplasmosis**.

Sulfadoxine/Pyrimethamine is used as **antimalarial drug**.

Urinary Tract Antiseptics

- **Urinary tract infections** (**UTIs**) are ***prevalent*** in **women** *of* **child-bearing age** and in the **elderly**.
- ***E. coli*** is the ***most common*** **pathogen**, causing *about* **80%** of ***uncomplicated upper*** and ***lower*** **urinary tract infections**.
- ***Staphylococcus saprophyticus*** is the ***second*** **most common bacterial pathogen** causing **urinary tract infections**.
- *In addition to* **Fluoroquinolones**, **Cotrimoxazole** and **Fosfomycin** **UTIs** may be ***treated with*** any **one** of a **group** of **agents** ***called*** **urinary tract antiseptics**.
- **Urinary tract antiseptics** ***do not*** **achieve antibacterial levels** in the **circulation**, but because they are ***concentrated*** in the **urine**, **microorganisms** at that **site** can be ***effectively*** **eradicated**.

Nitrofurantoin (Uvamin® retard)# (Macrodantin®) (Macrobid®)

Nitrofurantoin is the ***most common*** **urinary tract antiseptic**.

Formulations and ***absorption***;

Nitrofurantoin Monohydrate; ***well*** **absorbed** (***higher*** **dissolution**); ***more*** **GI distress**.

Nitrofurantoin Macrocrystals (**Uvamin® retard** & **Macrodantin®**) **absorbed** ***more*** **slowly** (***slower*** **dissolution**); ***less*** **GI distress**; **4** ***times*** **daily**.

75 mg Monohydrate + 25 mg Macrocrystal ***formulation*** (**Macrobid® 100**); ***twice*** **daily**.

Nitrofurantoin is **metabolized** & **excreted** ***rapidly*** (***no systemic*** **antibacterial action**)

Nitrofurantoin is **bactericidal** for ***many*** **Gram +ve** and **Gram -ve** ***bacteria***; such as ***Escherichia coli***, ***Staphylococcus saprophyticus***, ***Enterobacter*** **species**, ***Klebsiella*** **species** and ***Staphylococcus aureus***.

Pseudomonas aeruginosa and *many strains* of ***Proteus*** and *some* of ***Klebsiella*** are ***inherently*** **resistant** to **Nitrofurantoin**.

Doses; ***Take*** with **food** or **milk** to ***improve*** **absorption** and ***decrease*** **GI distress**.

- **Macrocrystals**; 50-100 mg orally every 6 hr for 7 days or for 3 days after obtaining sterile urine.
- **Monohydrate/Macrocrystals**; 100 mg orally every 12hr for 7 days or for 3 days after obtaining sterile urine.
- ***Children***; **>1 month-12 years** (**Macrocrystals** ***only***); 5-7 mg/kg/day orally divided every 6 hors for 7 days.

Pregnancy; **US FDA category B**.

Contraindications & ***precautions***; **#### PATIENT COUNSELLING ####**

Significant **renal insufficiency** (Creatinine Clearance < 60 mL/min).

Hepatic dysfunction or **cholestatic jaundice**.

Pregnancy at term (**38-42 weeks** of ***gestation***).

Neonates (**<1 month**).

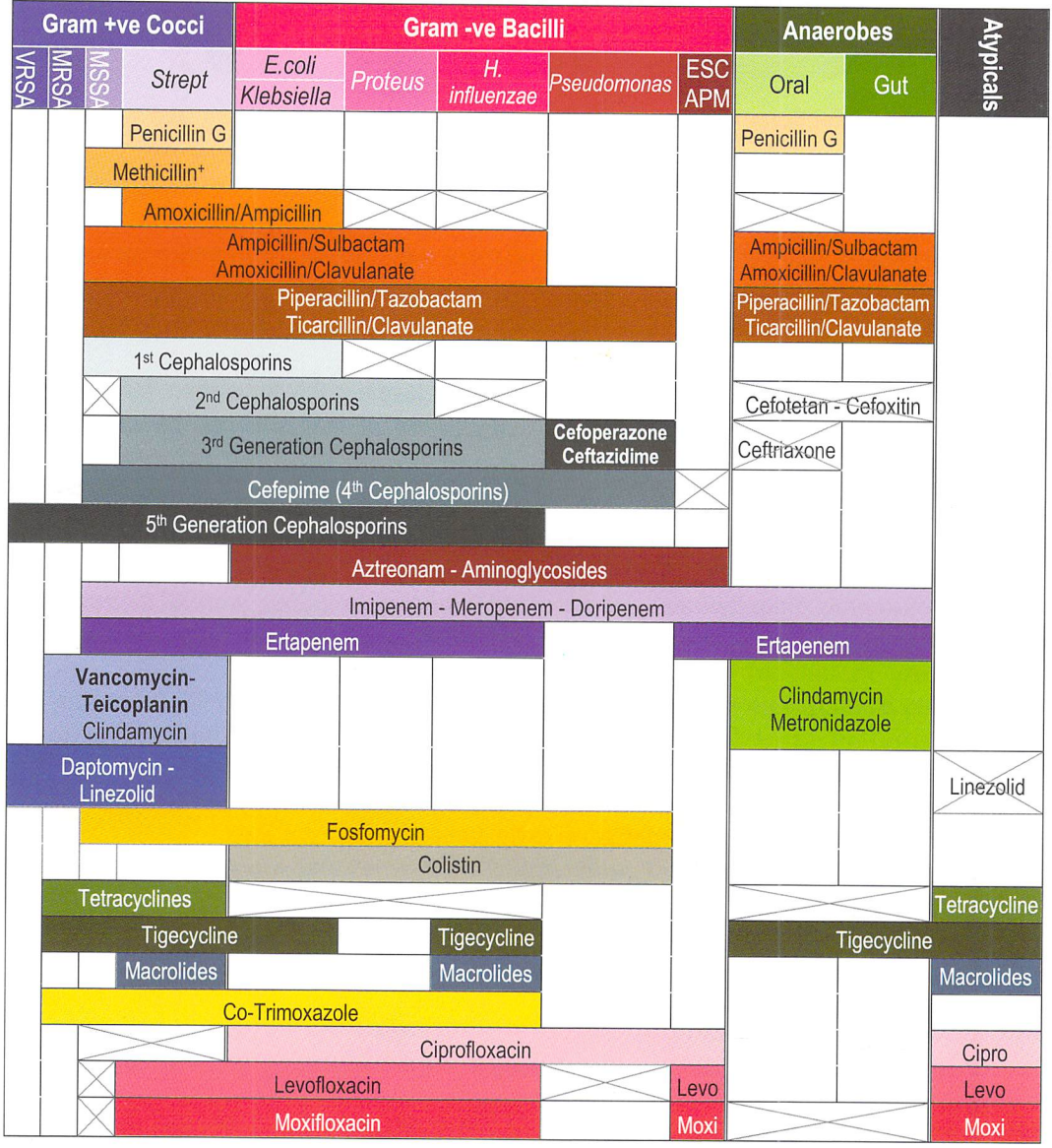
Caution in patients with **G6PD deficiency** (risk for hemolytic anemia).

Avoid **long-term use** in the **elderly** (risk for pulmonary toxicity).

#***Side effects***;

- ***Most common***; **GI disturbances** (**Nausea** and **vomiting**); ***Take*** with **food** or **milk**.
- ***Rare***; **pulmonary toxicity** and **neurologic problems**.

➢ Antibiotic Spectrum Guide:-



Coloured	***Good*** to ***excellent*** activity
	Moderate activity
	Little to ***no*** activity
Methicillin+	**Methicillin Group (Nafcillin - Oxicillin - Cloxacillin - Dicloxacillin - Flucloxacillin)**
ESCAPM*	*Enterobacter* spp., *Serratia* spp., *Citrobacter freundii*, *Aeromonas* spp., *Providencia* spp. and *Morganella morganii*.

➢ Topical Antibacterial Agents:-

Bacitracin	Polymyxin	Fusidic Acid	Mupirocin
Erythromycin	Clindamycin	Neomycin	Gentamicin
	Retapamulin	Dapsone	

Anti-Mycobacterial

- **Mycobacteria** are ***resistant*** to ***most*** **antibiotics**; *because* they **grow** ***more*** **slowly** *than* ***other*** **bacteria**, **antibiotics** that are ***most active*** *against* ***rapidly*** **growing cells** are ***relatively*** **ineffective**.
- **Mycobacteria cell walls** contain **mycolic acids**.
- **Antimycobacterial drugs** are used for the ***treatment*** of **mycobacterial infections**, ***including*** **tuberculosis** (*Mycobacterium tuberculosis*), **leprosy** (*Mycobacterium leprae*) and ***non*****tuberculous mycobacteria** (These species include; *Mycobacterium avium* **complex** (**MAC**) [*Mycobacterium avium-intracellulare*], *Mycobacterium chelonae*, *Mycobacterium abscessus*, *Mycobacterium kansasii*, and *Mycobacterium fortuitum*).

Anti-Tubercular Drugs

- **Tuberculosis** (**TB**) is an **infectious disease** *caused by* the **bacterium** *Mycobacterium tuberculosis*.
- **TB** is a ***multi-systemic*** **disease** affects ***mainly*** the **lungs**, ***but*** can also ***affect*** *other* **parts** of the **body**.
- The **classic symptoms** of ***active*** **TB** are a ***chronic*** **cough** with ***blood-containing*** **sputum**, **fever**, **night sweats** & **weight loss**. **TB treatment** ***generally*** includes **4** ***first-line*** **drugs**.
- **Second-line drugs** are *typically* ***less*** **effective**, ***more*** **toxic**, and ***less*** **extensively studied** and used for **patients** who ***cannot*** **tolerate** the ***first-line*** **drugs** or **who** are ***infected*** with ***resistant*** **TB**.

First-line

1) Rifamycins (RIF)

Rifampicin or Rifampin (RIF) (Rimactane®)#

- **Rifampicin** ***inhibits*** **bacterial DNA-*dependent* RNA polymerase**.

Rifampin is ***used*** in ***combination*** with **other anti-tuberculous drug** (**Isoniazid**, **Pyrazinamide** and **Ethambutol**);
  - **Rimactazide®**; **Rifampin 300 mg + Isoniazid 150 mg**.

Rifampicin is **potent** **CYP450 inducer**, ***leading*** to ***numerous*** **drug interactions**.

Uses; - **Mycobacterial Infections**; **10 mg/kg/day** ***orally*** OR **10 mg/kg** ***orally*** **twice weekly** (*usually* 600 mg/d; not to exceed 600 mg/day), ***must be*** **administered** *with* **Isoniazid** or ***other*** **antituberculous drugs** to **patients** with **active tuberculosis** to ***prevent*** **emergence** of **drug-resistant mycobacteria**.
  - **Neisseria Meningitidis Carrier**; 600 mg twice daily for 2 days.
  - **Haemophilus Influenzae *Type B* Infection Prophylaxis**; 600 mg/day orally/IV for 4 days.

Side Effects; # **Nausea**, **vomiting** and **rash** are the ***most common***.
  # **Orange-red** ***discoloration*** *of* **urine**.
  # **Hepatotoxicity** (transient abnormalities in liver function tests) & **Jaundice**; ***incidence*** of **hepatic dysfunction** ***increased*** when **Rifampicin** is co-administered with **Isoniazid**.
  # **Flu-like symptoms**, **acute renal failure**, **hemolytic anemia**, **thrombocytopenia** and **shock** *may occur* in ***high*** **doses**.

Rifabutin (Mycobutin®)

Rifabutin is *preferred for* Mycobacterium avium complex (MAC).
- MAC *infections* are *most* common in patients *with* human immunodeficiency virus (HIV), who are often taking antiretroviral therapy that is *metabolized by* CYP450. *Because* Rifabutin /less-potent CYP450 inducer *than* Rifampicin; Rifabutin is *preferred* in MAC.

Side effects; *Like* Rifampicin but can also *cause* neutropenia.

Rifapentine (Priftin®)

Rifapentine has activity *greater than* Rifampicin, and it also has a *longer* half-life, *may be used* once *weekly*.

Side effects; *Like other* Rifamycins but can also *cause* hyperuricemia.

2) Isoniazid (INH)

Isoniazid (INH)

Isoniazid, *also known as* Iso-Nicotinyl-Hydrazide (INH), *along with* Rifampicin, is one of the two *most important* TB drugs. # The structural *similarity* to Pyridoxine (Vitamin B6).

It is *never* given as a *single* agent in the *treatment of* active tuberculosis.

Isoniazid is a *drug of choice* for the treatment of latent tuberculosis; It can be given as monotherapy for latent (NOT Active) disease.

Elimination *Half-life*; *Pharmacogenomic metabolism*;
- *Fast* acetylators: 30-100 min. - *Slow* acetylators: 2-5 hrs.
- The proportion of fast acetylators is higher among people of Asian origin (and Native Americans) than those of European or African origin.
- Fast acetylators may require higher dosage than slow acetylators for equivalent therapeutic effects.

Isoniazid is active *only* against *Mycobacterium tuberculosis* and *Mycobacterium kansasii*.

Mechanism; Isoniazid *prevents* the synthesis of mycolic acids in the cell wall.

- *Doses*; - 5 mg/kg/d (300 mg orally once daily); Typical dose.
  - 10 mg/kg/d (600 mg orally once daily); For serious infections or in malabsorption.
  - 15 mg/kg dose (900 mg orally) once or twice-weekly.

Side effects;
  # Peripheral neuropathy (*dose-related*); 25–50 mg/d of Pyridoxine (Vitamin B6).
  # Hepatotoxicity (*Mild increase* liver function tests); *Like other* Rifamycins.
  # GI reactions; Nausea, vomiting, stomach pain & Hypersensitivity reactions.

Drug Interactions; Isoniazid can *reduce* metabolism of Phenytoin (CYP450 *inhibitor*).

3) Pyrazinamide (PZA)

Pyrazinamide (PZA) (P.T.B®)

Pyrazinamide (PZA) is a *synthetic* relative of Nicotinamide, only used in *combination* with Isoniazid, Rifampin and Ethambutol.

It is *generally* used *only* in the *first* 2 months of tuberculosis therapy.

Pyrazinamide is *well* absorbed orally, *widely* distributed in body tissues, *including* inflamed meninges (100%); effective *with* Rifampin and Isoniazid in tuberculous meningitis.

Pyrazinamide is active *only* against *Mycobacterium tuberculosis*.

- ***Doses*** (*# usually discontinued after **2 months** of a 6-month regimen #*);
  - **Daily therapy**; (Non-HIV); 15-30 mg/kg orally once daily; maximum: 2 g/day.
    - **OR**; **Twice weekly Directly Observed Therapy (DOT)**;50 mg/kg orally twice weekly; max: 2 g/d
  - **HIV-exposed/infected**; 20-40 mg/kg/dose once daily; maximum: 2 g/day.
  - **Renal Dose**; (CrCl < 30 mL/min or hemodialysis); 25-35 mg/kg per dose 3 times per week.

*# **Side effects***; **Hyperuricemia**, **Hepatotoxicity** and **Arthralgias** (**joint pain**).

- **N.B.**; If **hyperuricemia** is ***accompanied by*** **acute gouty arthritis**, **Pyrazinamide** ***should be*** **discontinued**.

4) Ethambutol (EMB)

Ethambutol (EMB) (Etibi®)

*# **Ethambutol*** is a ***first-line*** **drug** for the **treatment** of ***both*** **active tuberculosis** and **MAC infections** (***along with*** **Macrolides** and **Rifabutin** *for* **MAC infections**).

*# **Ethambutol*** ***like*** **others**, it's **used** **only** in ***combination*** in the *treatment of* **active tuberculosis**.

*# **Ethambutol*** can be **used** as a ***substitute*** for **Rifampin** in **patients** who are ***unable*** to take **Rifampin** ***during*** the **Continuation Phase** (***after*** **2 months**) of **active tuberculosis** ***therapy***.

*# **Spectrum***; ***Mycobacterium tuberculosis***, ***Mycobacterium avium*** & ***Mycobacterium kansasii***.

- ***Doses***; - **Daily therapy**; 15–25 mg/kg orally once daily.
  - **Directly Observed Therapy (DOT)**; 40 mg/kg orally twice a week or 30 mg/kg orally 3 times a week.

*# **Ethambutol*** is ***very*** **well** ***tolerated***, ***unlike*** **others** (**Rifampin**, **Isoniazid** and **Pyrazinamide**) it's ***not associated*** with **hepatotoxicity**.

*# # # **Side effects***; **Optic Neuritis** *OR* **Retrobulbar Neuritis**; **Ethambutol** = **Eyes**;
  - ***Diminished*** **visual acuity**.
  - ***Loss*** of **ability** to **discriminate** ***between*** **red** & **green** (**Red-green** ***color*** **blindness**).
  - ***Not recommended*** in **children < 5 years** old; difficult to monitor visual acuity.
  - **Vision tests** *needed for* **monitoring**.

- ***Other side effects***; **Peripheral neuropathy** and **hyperuricemia**.

Drug Regimen Example (2HREZ/4HR3)

Rifampicin; **RIF** or **R** - **Isoniazid**; **INH** or **H** - **Pyrazinamide**; **PZA** or **Z** - **Ethambutol**; **EMB** or **E**

- **2HREZ/4HR3**; *means*; **Isoniazid**, **Rifampicin**, **Ethambutol**, **Pyrazinamide** ***daily*** for **2 months**, *followed by* **4 months** of **Isoniazid** and **Rifampicin** given **3** ***times*** a **week**.

Second-line

- **Second-line drugs** are ***only*** **used** to **treat disease** that is ***resistant*** to **first-line therapy** (**Multi-Drug Resistant TB**; **MDR-TB**).
- **Second-line drugs** (WHO Tuberculosis Guidelines 4th edition);
  - ***Aminoglycosides***; **Streptomycin**, **Amikacin** and **Kanamycin**.
  - ***Fluoroquinolones***; **Ofloxacin**, **Levofloxacin** and **Moxifloxacin**.
  - ***Polypeptides***; **Capreomycin**. - ***Thioamides***; **Ethionamide** and **Prothionamide**.
  - ***Others***; ***p*-aminosalicylic acid**, **Cycloserine** and **Terizidone**.

Third-line

*# **Third-line drugs*** are drugs that ***may be*** **useful**, ***but*** have **doubtful** or **unproven** ***efficacy***:

*# **Third-line drugs*** (WHO Tuberculosis Guidelines 4th edition); **Clofazimine**, **Linezolid**, **Co-Amoxiclav**, **Thioacetazone**, **Imipenem/cilastatin**, *high-dose* **Isoniazid** & **Clarithromycin**.

Anti-Lepral Drugs

- **Leprosy** (**Hansen's disease**) is a ***chronic*** **infectious disease** caused by ***Mycobacterium leprae***.
- ***M. leprae*** **multiplies** ***slowly*** and ***incubation*** **period** of the **disease**, on ***average***, is **5 years**. *In some cases*; **symptoms** may *occur* ***within*** **1 year** but can also take as ***long as*** **20 years** to ***occur***.
- **Leprosy** ***mainly*** **affects**; **skin**, **peripheral nerves**, **mucosa** of **upper respiratory tract**, and *also* **eyes**.
- ***Prevalence***; **< 1 case** ***per*** **10,000** ***persons*** was achieved globally in the **year 2000**.
- **Leprosy** can be **treated** ***effectively*** with **Dapsone**, **Rifampicin** and **Clofazimine**.

A 24-year-old man with leprosy (1886)

Dapsone (Dapsone®)

Dapsone (**Di-amino di-phenyl sulfone**) is **structurally** ***related to*** the **sulfonamides** and **similarly** ***inhibits*** **dihydropteroate synthetase** in the **folate synthesis** ***pathway***.

Dapsone used in ***combination*** *with* **Rifampicin** and **Clofazimine** for the ***treatment of*** **leprosy**.

- It may also be **used** to ***prevent*** and ***treat*** ***Pneumocystis jiroveci*** **pneumonia** *in* **AIDS patients**.
- ***Other Uses***; **Dermatitis Herpetiformis**, **Toxoplasmosis** and ***topically*** in **Acne**.

Usual adult **dosage** in **leprosy**; **100 mg** ***daily*** in ***combination with*** other **antileprosy drugs**.

Common side effects; **Hemolysis** (with **favism**) and **Methemoglobinemia**.

Rifampicin

Rifampicin (*see previous topic*) is **only** ***given*** in ***combination*** in a **single** **monthly** ***dose*** of **600 mg** in **adult** ***with*** **Dapsone** and **Clofazimine**.

Clofazimine (Lamprene®)

Clofazimine is a ***phenazine dye***, *works by* ***inhibiting*** **bacterial DNA synthesis**.

It is **used** ***for***; - **Dapsone-sensitive leprosy**; **50 mg orally daily** in ***combination*** *with* **Dapsone** and **Rifampicin**.

- **Dapsone-resistant leprosy** or when patients are ***intolerant*** to **sulfones**; **100 mg** ***orally*** **daily** in ***combination*** *with* **1** or ***more*** other **antileprosy drugs**.

Clofazimine has some **anti-inflammatory** and **anti-immune** ***activities***, thus, **erythema nodosum leprosum** *may* ***not develop*** in **patients** ***treated*** *with* ***this*** **drug**.

Common side effects;

Skin discoloration *ranging from* **red-brown** to ***nearly*** **black** (75-100%).

GI intolerance; **Nausea**, **vomiting** and **stomach pain** (40-50%).

Ichthyosis and **dry skin** (8-28%).

Drug Regimen Example

MDT-Combi® packs; *donated by* **Novartis** for **WHO Multi-Drug Therapy** (**MDT**) ***regimens*** for **Leprosy**. *Each* **blister** of **MDT-Combi® pack** ***contains*** *treatment for* **4 weeks**.

Antifungal Drugs

Infectious diseases *caused by* **fungi** (**fungal infections** or **mycotic infections** or **mycoses**); are *often* **chronic** in **nature** and **many** of **mycoses** are **superficial** (*involve only* **outer layers** of the **skin** and **hair** , such as **Tinea versicolor**), while **others** ***may*** ***penetrate*** the **skin**, causing;
  # **Cutaneous** (**epidermis** and **nail**); *such as* **Tinea** (**ringworm**).
  # **Subcutaneous** (**dermis**, **subcutaneous tissues**, **muscle** and **fascia**); *such as* Debridement.
  # **Systemic infections** (*primarily* **lungs** and *may* other **organ systems**); *such as* Aspergillosis.

Serious systemic fungal infections ***less common*** **but** ***more serious*** and *increased* **incidence** in ***patients with chronic*** **immune suppression** ***due to*** **organ transplantation**, **cancer chemotherapy** or infection with **human immunodeficiency virus** (**HIV**); such as **aspergillosis**, **fungal endocarditis** and **fungal meningitis** (**cryptococcal meningitis**).

- ***Unlike Bacteria***;
  # **Fungi** are **eukaryotic**, with ***rigid*** **cell walls** *composed largely* of **Chitin** ***rather than*** **peptidoglycan**.
  # **Fungal cell membrane** *contains* **Ergosterol** *rather than* the **cholesterol** *found in* **mammalian membranes**.
  # **Cytochrome P450** (**CYP450**) enzyme (***C-14 α-demethylase***) in **fungal cell** *responsible for* ***demethylation*** of **Lanosterol** *to* **Ergosterol**.
  # **Fungal infections** are *generally* ***resistant to*** **antibiotics**, and *conversely*, **bacteria** are ***resistant to*** **antifungal agents**.

Antifungal agents or **Antimycotic agents** are **fungicide** or **fungistatic** ***used to treat*** & ***prevent*** **mycoses** such as; **athlete's foot**, **ringworm**, **candidiasis** (***thrush***), **serious systemic infections**

Systemic Antifungal for Systemic Infections

Polyene Antifungals

Amphotericin B (Fungizone®)# (AmBisome®)#

Amphotericin B ***remains*** the **drug of choice** for the *treatment of* ***several*** **life-threatening mycoses** (***broad*** **antifungal** ***spectrum*** and a **lack** of *available* **alternatives**).

Mechanism; ***Bind to*** **Ergosterol** in **cell membrane** → ***forming*** **pores** → **electrolytes** (*particularly* **potassium**) and **cell constituents** ***leak from*** the **cell** → **cell death**.

Amphotericin B is *nearly* ***insoluble*** in **water** and it *have* **renal** & **infusion toxicity**, therefore ***prepared*** in a ***several*** **formulations**; to ***improve*** **tolerability** and ***decrease*** **toxicity**, *but* may *show* ***different*** **pharmacokinetic characteristics** *compared to* **Conventional Amphotericin B**;
- **Amphotericin B Sodium Deoxycholate** (**ABD**).
- **Amphotericin B Colloidal Dispersion** (**ABCD**).
- **Amphotericin B Lipid Complex** (**ABLC**).
- **Liposomal Amphotericin B** (**LAmB**); ***high*** **cost**.
- ***Recently*** (2011); **AmbiOnp**; a ***novel*** **solid lipid nanoparticles** of **Amphotericin B** were ***formulated*** for **oral administration** for ***systemic*** **infections**.

- ***Uses***; - ***Antifungal***; **Life-threatening mycoses**, such as **Mucormycosis**, **Cryptococcal meningitis** and *certain* **aspergillus** and **Candidal infections**.
  - ***Antiprotozoal***; **Visceral Leishmaniasis** and **Amoebic Meningoencephalitis**.

- ***Dose*** (*Usual Adult*); "Double-check that dose of amphotericin B; which formulation are using"
  - **Conventional Amphotericin B**; 0.25-1 mg/kg IV infusion (***Should not exceed*** 1.5 mg/kg/d).
  - **Liposomal Amphotericin B** (**LAmB**); 3-6 mg/kg/day IV.
- **Amphotericin B** in ***diluted*** **solutions** it is ***sensitive*** to **light** and is ***inactivated*** at ***low*** **pH** (***should be protected from*** **light** *during* **administration**).

Side effects; **####### Amphotericin B PRECAUTIONS #######**

A) **Infusion-Reactions**; **Fever, chills, muscle spasms, vomiting, headache & hypotension.**
Can be attenuated by; # ***Slowing*** the **infusion rate**.
Using **initial dosing** ***regimen***.
Pre-medicating with **Acetaminophen, Hydrocortisone** and **Antihistamine**
Liposomal Amphotericin B has the ***lowest*** **incidence** of ***infusion-related*** **reactions**, while **Amphotericin B Colloidal Dispersion** has the ***greatest***.

B) **Nephrotoxicity**; **Renal tubular acidosis** and ***severe*** **hypokalemia** and **hypomagnesemia** (***Caution*** when **coadministration** with other drugs that cause **hypokalemia**; e.g., **corticosteroids, digoxin**).

C) **Others**; **Hepatotoxicity, Anemia & Thrombophlebitis** (decreased by adding heparin to infusion).

Antimetabolite Antifungals

Flucytosine or 5-Fluorocytosine (Ancobon®)#

Flucytosine or **5-Fluorocytosine** (**5-FC**) was *discovered* in **1957** *during* a **search for** ***novel*** **antineoplastic agents**, but it was ***without*** **anticancer properties**, and ***became*** apparent that it was a ***potent*** **antifungal agent**. # # It is ***specifically*** **used**, *together with* **Amphotericin B**. #

Mechanism; **Flucytosine** ***enters*** the **fungal cell** *via* a **cytosine permease** ***enzyme*** (***not found in mammalian cells***), **Flucytosine** is ***converted*** **intracellularly** ***first*** to **5-fluorouracil** (**5-FU**) and ***then*** to **5-fluorodeoxyuridine monophosphate** (**FdUMP**) and **Fluorouridine triphosphate** (**FUTP**), which ***inhibit*** **DNA, RNA** and **protein** ***synthesis***.

Amphotericin B ***increases*** **cell permeability**, ***allowing*** *more* **Flucytosine** to ***penetrate*** the **cell** and ***leading to*** **synergistic effects**.

Metabolism; *About* 10% by **intestinal bacteria** to **5-fluorouracil** (**5-FU**).

Uses; **Flucytosine** is ***not*** **used** *as* a **single agent** *because* of;
It has **synergistic effect** with *other* **agents**.
To ***avoid*** the **development** of ***secondary*** **resistance**.

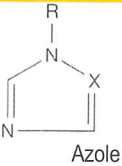
Flucytosine is **used** in ***combination*** *with*;
A) **Amphotericin B** for *treating* **Candidiasis** and **Cryptococcosis**.
B) **Itraconazole** (or **Fluconazole**) for *treating* **Chromoblastomycosis**.

Dose; **50-150 mg/kg/day orally** *divided* ***every*** **6 hours**.

Side effects;
GI disturbances (**nausea, vomiting**, and **diarrhea**); are ***common***.
Bone marrow suppression (**anemia, leukopenia** and **thrombocytopenia**); *result from* ***metabolism*** of **Flucytosine** to **5-fluorouracil** by ***intestinal*** **flora**.
Reversible **hepatic dysfunction** (***elevation*** of **serum transaminases** and **alkaline phosphatase**).

Azole (Triazole) Antifungals

- **Azoles** are a class of ***five-membered*** **heterocyclic compounds** ***containing*** a **nitrogen** ***atom*** and at ***least*** **one** other ***non-carbon*** **atom** (i.e. **nitrogen, sulfur** or **oxygen**) as ***part*** of the **ring**.
- **Azoles** that are *available for* **clinical use** are ***classified as*** either **Imidazoles** or **Triazoles** ***according*** to *number of* **nitrogen** ***atoms***.



X = C, imidazole
X = N, triazole
Azole Nucleus

Imidazoles (**Ketoconazole, Miconazole & Clotrimazole**); ***now*** **used** ***only*** **topically**.
Triazoles (**Fluconazole, Itraconazole, Posaconazole & Voriconazole**); **used systemically**.
Although **these drugs** *have* ***similar*** **mechanisms of action** and **spectra** of ***activity***, their **pharmacokinetics** and **therapeutic uses** ***vary*** **significantly**.
Ketoconazole is the ***first*** **azole**-*based* **oral** treatment of ***systemic*** **fungal infections**, in the ***early*** **1980s**, but ***now*** has ***largely*** been ***replaced*** due to *risk of* ***severe*** **liver injury, antiandrogenic** (**Ketoconazole** *shampoo may be beneficial* **alopecia**) and **antiglucocorticoid** and ***adverse*** **drug interactions**. ***Later***, **Triazoles** such as **Fluconazole** and **Itraconazole**, with ***improved*** **safety** *profile* were **developed**.

Mechanism; **Azoles** in ***general*** are **fungistatic**.
- **Azoles** are ***inhibit*** **C-14 α-demethylase** (***a*** **cytochrome P450 enzyme**), *thereby* ***blocking*** the ***demethylation*** of **Lanosterol** *to* **Ergosterol**, the ***principal*** **sterol** of **fungal membranes**.
- The ***inhibition*** of **Ergosterol** ***biosynthesis*** *disrupts* **membrane** ***structure*** and ***function***, which, in turn, ***inhibits*** **fungal cell** ***growth***.
- The ***selective*** **toxicity** of **Azoles** ***results*** *from* their ***greater*** **affinity** for **fungal** ***than*** for **human cytochrome P450** ***enzymes***.

Imidazoles *exhibit* a ***lesser*** **degree** of ***selectivity*** *than* the **Triazoles**, ***accounting*** for their ***higher*** **incidence** of **drug interactions** and **adverse effects**.

All **Azoles** ***inhibit*** the **hepatic CYP450 isoenzymes** (*especially* **CYP450 3A4**) to ***varying*** **degrees**; ***decrease*** **metabolism** of **other drugs**, ***leading*** to ***numerous*** **drug interactions**.

Fluconazole (Diflucan®)# (Fungican®) (Flucoral®)

Fluconazole was the ***first*** **member** of the **Triazole** class of ***antifungal agents***, was ***patented by*** **Pfizer** in **1981**, and in ***early*** **1990s** **Fluconazole** was a ***breakthrough*** in **antifungal pharmacotherapy**.

Fluconazole is ***highly*** **bioavailable** (***available*** in *both* **oral** and **IV** ***formulations***), with ***fewer*** **hepatic enzyme** ***interactions*** (***least*** **CYP450** ***effect***), with ***better*** **GI** ***tolerance*** and ***widest*** **therapeutic index** of ***all*** **Azoles**.

Antifungal spectrum; ***least*** **spectrum** of ***all*** **Triazoles** (***least*** **CYP450** ***effect*** of ***all*** the **Azoles**);
- # ***Highly*** **active** *against* ***most*** ***Candida*** **species** (*but* **NOT** ***Candida krusei*** or ***Candida glabrata***)
- # ***Good*** **activity** *against* ***Cryptococcus neoformans*** (e.g.; **Cryptococcal meningitis**).
- # ***Also*** **active** *against some* **dimorphic** ***fungi***.
- # ***No*** **activity** *against* ***Aspergillus*** **species**.

Uses; Dose is *same* in IV and oral administration; ***highly*** **bioavailable**.
- # **Vulvovaginal Candidiasis**; **150 mg orally** as a ***single*** **dose** (May repeated if complicated or recurrent)
- # **Oropharyngeal** *and* **Esophageal Candidiasis**; **200 mg IV** or **orally** on the ***first*** **day** *followed by* **100 mg IV** or **orally** ***once*** a **day**.
- # ***Systemic*** **Candidiasis** *and* **Cryptococcal Meningitis**; **400 mg IV** or **orally** on the ***first*** **day** *followed by* **200 mg IV** or **orally** ***once*** a **day**.
- # **Dermatomycosis** (*such as*; **tinea**); **150 mg** ***once weekly*** OR **50 mg** ***once*** **daily**; **2-4 weeks**. ; **Tinea pedis** (**athlete's foot**); *may require* up to **6 weeks**.
- # **Onychomycosis** (**fungal nail infections**); **150** to **300 mg orally** ***once*** a **week** (3 to 6 months).
- # ***Prophylaxis*** of **Candidiasis** with **Bone Marrow Transplantation** (**BMT**); **400 mg/day**.

Usual children dose; **6-12 mg/kg** on the ***first*** **day** *followed by* **3-12 mg/kg/day**; Duration and dosage
Side effects; depend on severity of infection.
- ***Most common***; **headache**, **nausea**, **vomiting** and **skin rashes**.
- **Hepatotoxicity** *can also* **occur** (***should be*** used with **caution** in *patients with* **liver dysfunction**).
- **QT interval** ***prolongation*** is *also possible*.

Itraconazole (Sporanox®)# (Itracon®) (Itrapex®)

Itraconazole is a ***second*** **member** of the **Triazole** class, it was ***invented*** in **1984**.

Itraconazole has a ***broader*** **spectrum** of **activity** *than* **Fluconazole** (**BUT** ***not as*** *broad as* **Voriconazole** or **Posaconazole**); It is **active** ***against*** ***Aspergillus***, which **Fluconazole** is ***not***.

Itraconazole is the ***drug of choice*** for; **Blastomycosis**, **Sporotrichosis**, **Histoplasmosis**, and **Onychomycosis**. It is ***rarely used*** for ***Candida*** and ***Aspergillus*** **species** *because* of the ***availability*** of ***newer*** and ***more*** **effective agents** (**Voriconazole** or **Posaconazole**).

- **Itraconazole** is ***available*** in **oral** and **IV** ***formulations*** (**IV** *has been* ***discontinued***).

Oral dosage forms (**capsules** have ***lower*** **bioavailability** than **oral solution**);
- # **Oral solution**; ***should be*** **taken** on an **empty stomach**, as **food** ***decreases*** the **absorption**.
- # **Capsules**; ***should be*** **taken** ***with*** **food**, and ***ideally*** an **acidic beverage** (**orange juice** or **cola**) to ***increase*** **absorption**; **acid suppression** ***therapy*** like **PPIs**; ***decrease*** **absorption**;

Sporanox® capsules *contain tiny* 1.5 mm pellets *with complex* three-layer structure to *increase* absorption and bioavailability (Korean Patent Laid-open No. 10-2001-2590);

1) Inner layer; Itraconazole 1 part by weight.
2) Mid-layer; Citric acid 0.25 part by weight.
3) Outer layer; Hydroxypropylmethylcellulose 0.25 part by weight.

- It is > 99% *protein-bound* and penetrates *poorly* into CSF (*NOT* preferred in meningitis)

Antifungal spectrum;

Highly active *against most* of *Candida* and *Aspergillus* species, *Cryptococcus neoformans*, and *many* dimorphic fungi (Itraconazole is the azole of choice for dimorphic infections).

Good activity *against Candida krusei* and *Candida glabrata*.

Uses; Blastomycosis, Sporotrichosis, Histoplasmosis and Onychomycosis.

Usual dose; - *Adult*; 100-200 mg twice a day. - *Children*; ≥3 years: 3-5 mg/kg/day.

Side effects; - *Most common*; nausea, vomiting and rash.
- Hypokalemia, hypertension, edema and headache are *common*.
- Hepatotoxicity *can* also occur.

Negative inotropic effect *can* also occur (*should be* avoided in patients *with* heart failure).

Voriconazole (Vfend®)# (Vorifend®) (Vorigrand®)

Voriconazole is *similar* to Itraconazole in its *spectrum*, having *excellent* activity *against Candida* (*including* Fluconazole *resistant* species such as *Candida krusei*), *Cryptococcus neoformans*, *Aspergillus*, *Scedosporium* and *Fusarium* species (Voriconazole is the *drug of choice* for invasive aspergillosis; *less toxic* than Amphotericin B), and *many* dimorphic *fungi*.

Unlike Itraconazole, Voriconazole is *well* absorbed and *available* in *both highly* bioavailable oral *formulation* and IV admixture (*exceeding* 95%).

Voriconazole IV admixture with Sulfobutylether β-Cyclodextrin (SBECD) is *restricted* in patients with renal insufficiency (CCL <50 mL/min); SBECD *accumulate* in renal dysfunction.

Uses; Invasive Aspergillosis, Candidemia, Esophageal Candidiasis & *Serious* Mycoses.

- *Usual* dose; 6 mg/kg IV *every* 12 hours on day 1, then 4 mg/kg IV *every* 12 hours (IV therapy should continue for at least 7 days), oral dose 100 mg (< 40 kg) to 200 mg (> 40 kg) *every* 12 hrs

Side effects; - *Most common*; Visual disturbances (up to 28%).
- *Very common*; Skin rashes, phototoxicity, headaches, peripheral edema, fever, *trouble* breathing, nausea, vomiting and diarrhea.

Posaconazole (Noxafil®)#

Posaconazole is a *broad-spectrum* triazole antifungal, *structurally similar* to Itraconazole, that is *more* active *against many* fungi.

Posaconazole is available as an oral suspension, oral tablet or IV formulation; *absorption* is *improved* when taken *with high* fat meals (*increases* concentration by 4 times *compared to* fasting *state*); acidic beverage (orange juice or cola) *increase* absorption; PPIs *decrease* absorption.

Posaconazole is the *broadest* spectrum *member* of the azole family, with *activity against most* species of *Candida*, *Aspergillus* and *Zygomycetes*.

Uses; - Invasive aspergillosis and candidiasis.
- Oropharyngeal candidiasis (OPC); *including refractory* to Itraconazole and/or Fluconazole.

- *Usual* dose; 300 mg orally *twice* a day on the *first* day, *then* 300 mg orally *once* a day.

Side effects; *Most common* (> 10%); Headache, fever, nausea, diarrhea, anemia, hypokalemia and hypomagnesemia.

Isavuconazole (Cresemba®)

- Isavuconazonium sulfate is a *prodrug* for Isavuconazole.

Isavuconazole is the *newest* triazole antifungal; FDA approval in March 2015.

It is *used* to treat invasive aspergillosis & invasive mucormycosis (Zygomycosis).

- *Dose*; - *Loading*; 1 vial (372 mg) IV or 2 capsules (372 mg) orally, every 8 hours for 6 doses (48 hours).
- *Maintenance*; 1 vial (372 mg) IV or 2 capsules (372 mg) once daily.

Echinocandins

- **Echinocandins** are the ***newest*** **class**, **Caspofungin** was the ***first*** **drug**; **approved** in **2001**.
Echinocandins are ***large*** **cyclic peptides**, So they are *available* ***only*** in **IV** ***formulations***.
Echinocandins have ***potent*** **activity** ***against*** ***Aspergillus*** and ***most*** ***Candida*** **species**.
Echinocandins cause ***mild*** **Histamine**-*mediated* **infusion**-*related* **reactions** (**flushing**).

Caspofungin (Cancidas®)#

Uses;
- **Invasive Candidiasis**, *including* **Candidemia**; ***first line***.
- **Invasive Aspergillosis** in **patients** ***refractory to*** or ***intolerant*** of *other* **therapies** (e.g., **Amphotericin B** or **Itraconazole**); ***second line***.

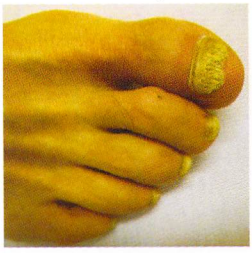
- ***Dose***; 70 mg IV infused over 1 hr in day first day, then 50 mg IV infused over 1 hr per day.
Warning;
- **Hypersensitivity** and **Anaphylaxis**.
- ***Do not*** **use** **Dextrose** ***diluents*** (**Caspofungin** is not stable).
- ***Do not*** **use** *with* **Cyclosporine** (unless benefits outweigh risks).
- ***Not*** for **bolus administration**.

Micafungin (Mycamine®)# | Anidulafungin (Ecalta®)# (Eraxis®)

Uses; **Invasive Candidiasis**, *including* **Candidemia**.
- ***Dose***;
- **Micafungin**; 100-150 mg/day IV infusion (***only*** **echinocandin** ***not require*** a **loading dose**).
- **Anidulafungin**; 200 mg IV infusion in first day, then 100 mg/day IV.
N.B.; **Anidulafungin** is ***not*** **metabolized** by **liver** ***can be*** *used* in **severe hepatic dysfunction**.
N.B.; **Micafungin** ***not*** **used** *with* **Sirolimus** and **Nifedipine**.

Systemic Antifungal for Cutaneous Mycotic Infections

- **Cutaneous fungal** (**mycotic**) **infections** are ***non***-**invasive infections** of the **skin**, **hair** or **nails**;
- **Dermatophytosis** (**skin** and **hair**);
- **Tinea Corporis** (**ringworm**).
- **Tinea Faciei** (**facial ringworm**).
- **Tinea Cruris** (**jock itch**).
- **Tinea Pedis** (**athlete's foot**).
- **Tinea Capitis** (**scalp ringworm**).
- **Tinea Manuum** (**ringworm of the hands**).
- **Onychomycosis** (**tinea unguium**); **nail fungal infection**.


Onychomycosis

- **Cutaneous infections** are *usually* ***treated with*** **topical agents**, but ***persistent*** and ***non-responsive*** **infections** are ***better*** **treated** with **oral antifungal agents**.

Griseofulvin (Ultragriseofulvin®)#

NOW **Griseofulvin** has been ***largely*** *replaced by* **oral** **Terbinafine** for the ***treatment of*** **Onychomycosis**, although it is ***still used*** for **Dermatophytosis**.
Formulations; - **Microsize** OR **Ultramicrosize**; **capsules**, **tablets** or **suspension**.
Absorption; - **Ultramicrosize Griseofulvin**; **absorption** is almost ***complete***.
- **Microsize Griseofulvin**; **25-70%** of **oral dose** (***enhanced by*** **fatty meal**).
Dose; 2–6 weeks for **Dermatophytosis** (skin/hair infection), 4-6 months for **Onychomycosis** (nail infection).
- ***Microsize***; 1000 mg/day (***Ultramicrosize***; 660 to 750 mg/day); orally in 2 to 4 divided doses.
Side effects; **Rash**, **urticaria**, **headache**, **GI disturbance** and **oral thrush**.
Contraindicated in ***patient with*** **porphyria**.

Terbinafine (Lamisil®)# (Terbin®)

Terbinafine is an *Allylamines antifungal* used *orally* or *topically* act by ***inhibiting*** squalene epoxidase → ***blocking*** the **biosynthesis** of **ergosterol** (not act on CYP450).

- Terbinafine is the *drug of choice* for ***treating*** Onychomycosis;
  - **Better tolerated**.
  - ***Shorter*** **duration** of **therapy**.
  - ***More*** **effective**.

Uses and *Doses*;

- **Onychomycosis** (*drug of choice*) 250 mg once daily for 6 weeks (fingernail) or 12 weeks (toenail).
- **Tinea Corporis, Tinea Cruris**; 250 mg/day orally in single dose or divided every 12hr for 2-4 weeks.
- **Tinea Pedis** (Off-label); 250 mg/day orally in single dose or divided every 12hr for 2-6 weeks.
- **Sporotrichosis, Lymphocutaneous** and **Cutaneous** (Off-label); 500 mg/day PO q12hr for 2-6 weeks; treat for additional 2-4 weeks after resolution of all lesions (resolution may take 3-6 months).

Pregnancy; **Category B** # *Lactating women*; ***Accumulates*** in **breast milk** and ***should not*** **used**.

Side effects; **Headache**, **GI disturbances** and **rash**.

Terbinafine is used with ***caution*** in **renal** and **liver** ***impairment***.

Topical Antifungals

Polyene Antifungal

Nystatin (Mycostatin®)# (Fungistatin®)

Nystatin is a ***polyene*** **antifungal**, *similar to* Amphotericin B.

Nystatin is *negligibly* ***absorbed*** from **GIT**, and *not* **used** ***parenterally*** *due to* **systemic toxicity**; Liposomal Nystatin is also available *off-label* for **invasive fungal infections**.

Uses;

* **Oropharyngeal Candidiasis**;

- **1-12 months**; 200,000 *units* 4 *times* daily.
- **1-18 years**; 400,000 to 600,000 *units* 4 *times* daily.

* **Intestinal Candidiasis**;

- **Oral tablets**: 500,000-1,000,000 *units* every 8 hours.
- **Powder**: 1/8 to 1/4 teaspoonful in 1/2 cup of water (500,000-1,000,000 units) orally every 8 hrs.

Azole (Imidazole) Antifungals

Ketoconazole (Nizoral®)	**Miconazole** (Daktarin®)	**Econazole** (Pevaryl®)
Isoconazole (Travocort®)	**Clotrimazole** (Canesten®)	**Oxiconazole** (Tinox®)
Tioconazole (Trosyd®)	**Sertaconazole** (Dermofix®)	**Butoconazole** (Gynazole-1®)
Sulconazole (Exelderm®)	**Terconazole** (Terazol®)	**Bifonazole** (Mycospor®)

Topical **Imidazoles** have a ***variety*** of **uses**, *including*; **tinea corporis, tinea cruris, tinea pedis** and **oropharyngeal** and **vulvovaginal candidiasis**.

Allylamine Antifungals

Terbinafine (Lamisil®)#	**Naftifine** (Exoderil®)#
Butenafine (Derfina®)#	**Amorolfine** (Loceryl nail lacquer®)#

They are ***used for*** **topical treatment** of **tinea infections**.

Loceryl nail lacquer® is used *for* **fungal nail infection** ***once*** or ***twice*** **weekly**.

Others

Ciclopirox (Batrafen®)#	**Tolnaftate** (Tineacure®)#	**Clioquinol** (Betnovate-C®)#

Ciclopirox and **Tolnaftate** are used for **cutaneous mycotic infections**.

Clioquinol or **Iodochlorhydroxyquin** is an ***antifungal*** and ***antiprotozoal drug***.

Antiviral Drugs

Antivirals for Herpesvirus Infections

Agents for Herpes Simplex Virus (HSV) and Varicella-Zoster Virus (VZV)

Acyclovir (Zovirax®)#

- **Acyclovir** (**Acycloguanosine**) is the ***prototypic* antiherpetic drugs**.
Acyclovir *bioavailability* is ***low***; 15–30%.
Uses; - **Genital Herpes**; for 7-10 days (duration of therapy).
- **Herpes Simplex Virus**;
- **HSV Encephalitis**; 10 days; up to 14-21 days.
- **Neonatal HSV Infection**; up to 14-21 days (*according to site of infection).*
- **HSV Mucocutaneous Infection** (**Herpes Labialis**); for 5-10 days.
- **Herpes Zoster** (**Shingles** and **Chickenpox**); for 7-10 days.
- ***Dose***; - ***Adult***: - **Oral**; **200 mg 5 times daily - 400-800 mg 2-4 times daily**; *according to infection.*
- **IV**; **10 mg/kg IV** *every* **8 hours**.
- ***Child***: - **Oral**; **200 mg Susp**. (10-20 mg/kg/dose) **4 times daily**; *according to infection.*
- **IV**; **10-20 mg/kg IV** *every* **8 hours**.

"**Dose *must be* adjusted** in *patient with* **renal failure**"

- ***Side effects***; ***Depend on*** the **route of administration**;
- ***Topical***; **local irritation**.
- ***Oral***; **malaise**, **headache**, **diarrhea**, **nausea** and **vomiting**.
- **IV**; **injection site reactions**, **nausea**, **vomiting** and ***reversible* renal dysfunction** or **neurologic effects** (may occur at high doses).
- ***Pregnancy***; **Recent study found *no* evidence** of ***increased* birth defects** (**Category**; **B**).

Valacyclovir (Valtrex®)# (Valtrovir®) (Valysernex®)

Valacyclovir is an **L-valyl ester** of **Acyclovir**. It is ***rapidly*** *converted to* **Acyclovir** after **oral administration** by the **liver** (first pass enzymatic hydrolysis) and **intestine**, **serum levels** are **3** to **5** ***times* greater *than* oral Acyclovir** and **oral bioavailability** is ~ **55%**.
Uses; - **Herpes Labialis** (**Cold Sores**); 2 g orally every 12 hrs for 1 day.
- **Genital Herpes**;- *First episode*; 1 g orally every 12 hrs for 10 days.
- *Recurrent*; 500 mg orally every 12 hrs for 3 days.
- **Herpes Zoster**; 1 g orally every 8 hours for 7 days.

"**Dose *must be* adjusted** in *patient with* **renal failure**"

- ***Side effects***; ***same as* Acyclovir**.

Penciclovir (Pandrocear®) (Ploref®)

- **Penciclovir** is **absorbed *poorly***; used ***only*** as a ***topical* treatment** *for* **Herpes Simplex Labialis**.

Famciclovir (Famvir®)# (Propencivir®)

- **Famciclovir** is a ***prodrug*** of **Penciclovir**, to ***improve* oral bioavailability** (**77%**).
Uses; - **Herpes Labialis**; - First episode; 250 mg orally every 8 hrs for 7-10 day.
- Recurrent; 1500 mg orally once; initiate therapy at first sign.
- **Genital Herpes**; - First episode; 250 mg orally every 8 hrs for 7-10 day.
- Recurrent; 1000 mg orally every 12 hrs; for 1 day.
- **Herpes Zoster**; 500 mg orally every 8 hrs; for 7 day.

"**Dose *must be* adjusted** in *patient with* **renal failure**"

- ***Side effects***; **headache**, **nausea** or **diarrhea** *may occur*.

Docosanol (Abreva®) (Docozan®)

- **Docosanol** is **used *topically*** to ***reducing* duration** of **cold sores** or **fever blisters** *on* **face** or **lips**

Trifluridine (Viroptic®) (Lonsurf®)

- **Trifluridine eye *drop*** is used **kerato-conjunctivitis** and **keratitis** *due to* **HSV 1** and **2**.

Agents used to treat Cytomegalovirus (CMV)

Ganciclovir (Cytovene®)# (Ganvir®)#

Ganciclovir is an *acyclic* guanosine *analog* (*analog of* Acyclovir that has greater activity *against* CMV *up to* 100 times *greater than* that of Acyclovir).

Uses;

- CMV Retinitis;
  - *Initial*: 5 mg/kg IV at a constant rate over 1 hour, every 12 hours for 14 to 21 days.
  - *Maintenance*:
    - IV; 5 mg/kg IV at a constant rate over 1 hour once a day, 7 days/week OR 6 mg/kg IV once a day, 5 days/week.
    - Oral: 1000 mg 3 times a day or 500 mg 6 times a day (every 3 hours while awake) with food.
- CMV *Prophylaxis*;
  - HIV Patients; 1000 mg orally 3 times a day with food.
  - Transplant Patients;
    - *Initial*; 5 mg/kg IV over 1 hour every 12 hours for 7 to 14 days.
    - *Maintenance*;
      - IV: 5 mg/kg IV once a day, 7 days/week or 6 mg/kg IV once a day, 5 days/week.
      - Oral: 1000 mg orally 3 times a day with food.
- CMV Colitis or Esophagitis in HIV Patients (Off-label).

"Dose *must be* adjusted in *patient with* renal failure"

Side effects; Myelosuppression (Neutropenia, Thrombocytopenia).

Ganciclovir is teratogenic (embryotoxic).

Valganciclovir (Valcyte®)#

Valganciclovir is an L-valyl ester *prodrug* of Ganciclovir, It is *rapidly converted to* Ganciclovir after oral administration, to *improve* oral bioavailability of Ganciclovir.

Uses; - CMV Retinitis; - *Induction*: 900 mg orally twice a day for 21 days.

- *Maintenance*: 900 mg orally once a day.
- CMV *Prophylaxis*; 900 mg orally once a day.
- CMV Colitis or Esophagitis in HIV Patients (Off-label).

"Dose *must be* adjusted in *patient with* renal failure"

Side effects; Vomiting, abdominal pain, diarrhea, headache, insomnia, peripheral neuropathy, retinal detachment and myelosuppression.

Cidofovir (Vistide®)

Administration; - IV and Intravitreal (injection into vitreous humor between lens and retina).

- Intravitreal of Cidofovir is *associated with* risk of hypotony and uveitis.

Uses; - CMV Retinitis; - *Induction*; 5 mg/kg via IV infusion once a week for 2 consecutive weeks.

- *Maintenance*; 5 mg/kg via IV infusion once every 2 weeks.

" *Must* administer Probenecid *orally* & IV normal saline with *each* dose of Cidofovir to *reduce* risk of nephrotoxicity"

- Smallpox Vaccine Reaction (Off-label); 5 mg/kg via IV infusion once may be repeated 1 week later.

Major side effects; *Dose-dependent* Nephrotoxicity (*reduced* with pre-hydration using normal saline and *blocks* active tubular secretion by *high-dose* of Probenecid), proteinuria, azotemia, metabolic acidosis, and Fanconi's syndrome *may occur*.

Foscarnet (Foscavir®)

- *Administration*; IV and Intravitreal (poorly absorbed orally and GI intolerance).

Uses; - CMV retinitis, CMV gastroenteritis and acyclovir-*resistant* HSV infections.

- *Dose* in CMV retinitis; - *Induction*; 90 mg/kg IV (90- to 120-minute infusion) every 12 hours or 60 mg/kg IV (minimum 1-hr infusion) every 8 hrs over 2-3 weeks depending on clinical response.
  - *Maintenance*; 90 to 120 mg/kg IV (2-hour infusion) once a day.

"Dose *must be* adjusted in *patient with* renal failure"

Side effects; Nephrotoxicity, anemia, nausea fever, electrolyte *imbalance* and genital ulcer.

Antivirals for Viral Respiratory Infections (VRIs)

Neuraminidase Inhibitors (NAIs)

Oseltamivir (Tamiflu®)# (Taminil-N) | Zanamivir (Relenza®)

Oseltamivir and **Zanamivir** are ***effective*** **against** ***both*** **type A** and **type B influenza viruses**.
Benefits; - **Administration** ***before*** **exposure**; ***prevent*** **infection**.
- ***Early*** **administration** *within* **24** to **48 hours** *after* the ***onset*** of **symptoms**; ***modestly*** *decrease* **intensity** and **duration** of **symptoms**.
Dose; - **Oseltamivir**; ***Duration of therapy***: **5 days**;
- <15 kg: 30 mg *orally* twice daily.
- 15-23 kg: 45 mg *orally* twice daily.
- 23-40 kg: 60 mg *orally* twice daily.
- >40: 75 mg *orally* twice daily.
- **Zanamivir**; **10 mg** (**2** ***inhalation tab.***) **twice** for **5 days**.
Side effects; - **Oseltamivir**; **GI discomfort** and **nausea** (can ***decreased*** by **taking** *with* **food**).
- **Zanamivir**; **Headache**, **throat/tonsil pain** and **cough**.
- **Zanamivir** ***should be*** **used** *with* **caution** in **asthma** or **COP disease** (**bronchospasm** *may occur*).

Peramivir (Rapivab®) | Laninamivir (Inavir®)

- **Peramivir** and **Laninamivir** are a ***new agents*** in **NAIs**.
- **Peramivir** was ***approved*** for **IV** **administration** in 2014 for treatment of **Influenza**.
- **Laninamivir** was ***approved*** for **Influenza** in **Japan** (***treatment*** in 2010 and for ***prophylaxis*** in 2013) under the name **Inavir®** dry powder for **inhalation**.

Baloxavir Marboxil (Xofluza®)

- 24/10/2018; FDA approved **Baloxavir Marboxil** (Xofluza®) tablets, a drug that reportedly can kill influenza types A and B in as little as 1 day among some patients **(ONLY one tablet)**.

Adamantane Derivatives

Amantadine (PK-Merz®)# (Symmetrel®)# | Rimantadine (Rymanta®)

Amantadine and **Rimantadine** are **active** ***against*** **Influenza A** ***only***, due to ***widespread*** **resistance**, they are *usually* ***not*** **recommended**.
- **Amantadine** is an ***antiparkinsonian drug***.
Dose; **Influenza A**; - **Amantadine**; 100 mg twice daily or 200 mg once.
- **Rimantadine**; 100 mg twice daily.
Side effects; - **GI intolerance**.
- **Amantadine**; **CNS side effects**; **insomnia**, **dizziness** and **ataxia**.
- **Tromantadine** (**Viru-Merz®**) is ***another*** ***Adamantane derivative*** *available as* **topical gel** for **HSV**.

Ribavirin

Ribavirin

Used for; - **Respiratory Syncytial Virus** (**RSV**) ***infection*** (***Inhalation***).
- **Hepatitis C** (in combination with other antiviral drugs).
- **Viral Haemorrhagic Fever**.

- ***Oral***; **bioavailability** 64%, ***increased*** ***with*** **fatty meal**.
Dose; for **Hepatitis C** (Genotype 1, 4); - < **75 kg**: 1000 mg/day orally divided every 12 hours.
- ≥ **75 kg**: 1200 mg/day orally divided every 12 hours.
Side effects; - ***Dose-dependent*** *transient* **anemia**; **monitoring** is ***essential***.
- **Nausea**, **fatigue**, **headache**, **myalgia**, **arthralgia** and **insomnia**.
FDA "BLACK BOX" warnings;
Should not be **used** ***alone*** for **chronic hepatitis C virus infection**.
Hemolytic anemia; ***Should not*** be **used** in ***unstable*** **cardiac disease** (**Hb monitoring**).
Teratogenic (**Category X**); ***Avoid*** in **women** and **men** who are ***pregnant*** and ***after*** **6 months** of **therapy**.

Influenza Vaccine (Vaxigrip®)#

Dose; # 6 to 35 months (*3 years*); 0.25 mL *once* yearly (second injection 0.25 mL with 1 month *interval only* in first time of vaccination).
3 to 8 years; 0.5 mL *once* yearly (second injection 0.5 mL with 1 month *interval only* in first time of vaccination).
≥ 9 years; 0.5 mL *once* yearly.

Antivirals *for* Hepatitis Viruses

Antivirals *for* Hepatitis B Virus (HBV)

Interferon alpha (IFN-α)

- 3 *forms* of Interferon; - Alpha (α); Chronic hepatitis B & C, Genital warts, *some types* of Leukemia and Kaposi sarcoma.
- Beta (β); Multiple sclerosis.
- Gamma (γ); Chronic Granulomatous Disease.

Dose;
- PegIFN-α-2a *for* Hepatitis C (NOT USED ALONE) & Hepatitis B; 180 mcg SC once *weekly*.
- PegIFN-α-2b *for* Hepatitis C (NOT USED ALONE); 1.5 mcg/kg SC once *weekly*.
- IFN-α-2b *for* Hepatitis C (NOT USED ALONE); 3 million IU IM or SC 3 times a *week*.
and Hepatitis B; 30-35 million IU *per week* IM or SC, either as;
- 5 million IU once a day OR as 10 million IU 3 *times* a *week*.

"PegIFN-α *may* use as monotherapy *in* Chronic Hepatitis C (CHC) patients *if* contraindications or *significant* intolerance to antiviral drugs"

Side effects;
- Flu-like symptoms (fever, chills, myalgias, arthralgias and GI disturbances);
- Typically occurs *within* 6 hours *after* dosing, occur in *more than* 30% of patients during the first week of therapy and *tends to* resolve *upon continued* administration.
- Fatigue, mental depression and weight loss.

Lamivudine (Zeffix®)# (Epivir®)	**Adefovir** (Hepsera®)#
Entecavir (Baraclude®)	**Telbivudine** (Sebivo®) (Tyzeka®)
Tenofovir Disoproxil Fumarate (TDF) (Viread®)	
Tenofovir Alafenamide (Vemlidy®)	

- Lamivudine (Zeffix®)#;
Dose; - HIV Infection; 150 mg orally *twice* a day OR 300 mg orally *once* a day.
- Chronic Hepatitis B; 100 mg orally *once* a day.
- Adefovir (Hepsera®)#; Chronic Hepatitis B;
Dose; 10 mg orally *once* a day.
- Entecavir (Baraclude®); Chronic Hepatitis B;
- ***Dose***; - *Nucleoside-inhibitor-therapy-naive* (≥16 years): 0.5 mg orally *once* a day.
- Lamivudine-*refractory* (≥16 years): 1 mg orally *once* a day.
- *Decompensated* liver disease (≥16 years): 1 mg orally *once* a day.
- Telbivudine (Sebivo®) (Tyzeka®); Chronic Hepatitis B;
- ***Dose***; 600 mg orally *once* a day (with or without food).
- Tenofovir Disoproxil Fumarate (TDF) (Viread®); HIV Infection and Chronic Hepatitis B;
- ***Dose***; 300 mg orally *once* a day.
- In 2016 Vemlidy® (Tenofovir Alafenamide), was *approved* for HIV Infection and Chronic Hepatitis B.
- ***Precautions***;
- Doses *must be* adjusted in *patient with* renal failure.
- Lactic acidosis, hepatomegaly and *severe acute* Exacerbation of hepatitis B *may result*.

Hepatitis B Vaccine (Engerix-B®)#

Dose; Engerix-B®; # < 19 years; 3 doses (0.5 mL or 10 mcg *each*); 0-, 1-, 6-month.
> 20 years; 3 doses (1 mL or 20 mcg *each*); 0-, 1-, 6-month.

- Hepatitis B vaccine schedules for newborn infants (R; Advisory Committee on Immunization Practices; ACIP);
  A) Single antigen + Combination vaccine (2017 Vaccination Schedule in Egypt);
  - 4 doses of vaccine; 0-(*within* 12 hours), 2-, 4-, 6-month.
  - Infants born to HBsAg-*positive* mothers: 0.5 mL IM *within* 12 hours of birth PLUS hepatitis B immune globulin (HBIG), *followed by*; 3 additional hepatitis B vaccine doses; 2-, 4-, 6-month.

  B) Single-antigen vaccine;
  - 3 doses of vaccine; 0-(*within* 12 hours), 1-2, 6-18 month.
  - Infants born to HBsAg-*positive* mothers: 0.5 mL IM *within* 12 hours of birth PLUS hepatitis B immune globulin (HBIG), *followed by*; 2 additional hepatitis B vaccine doses; 1-2, 6-month.

Hepatitis A Vaccine (Havrix®)#

Dose; Havrix®; # Children and adolescents; 2 doses (0.5 mL); 0-, 6 to 12-month.
Adult; 2 doses (1 mL); 0-, 6 to 12-month.

Hepatitis B + Hepatitis A Vaccine (Twinrix®)#

Dose;
- Twinrix®; # > 18 years (approved only); 3 doses (1 mL); 0-, 1-, 6-month.
- Twinrix® Paediatric (1 year up to and including 15 years); 3 doses IM (1 mL); 0-, 1-, 6-month.

Antivirals *for* Hepatitis C Virus (HCV)

Interferon alpha-2b (IFN-α-2b) + Ribavirin

- In 1998 FDA *approves* Rebetron®; combination therapy *containing*; Rebetol® (Ribavirin) capsules and Intron® A (Interferon alfa-2b, *recombinant*) injection for the *treatment* of HCV;
- *Dose*; - Intron® A (Interferon alfa-2b); 3 million units SC 3 *times* weekly, PLUS
  - Rebetol® (Ribavirin); - <75 kg; 1000 mg/day. - ≥75 kg; 1200 mg/day.

PEG-Interferon alpha-2b (PegIFN-α-2b) + Ribavirin

- PEG-Intron® (PegIFN-α-2b) PLUS Rebetol® (Ribavirin) was also *approved* in 2001 to treat HCV.
- *Dose*; - PEG-Intron® (PegIFN-α-2b); 1.5 mcg/kg SC once *weekly*, PLUS
  - Rebetol® (Ribavirin); - <75 kg; 1000 mg/day. - ≥75 kg; 1200 mg/day.

PEG-Interferon alpha-2a (PegIFN-α-2a) + Ribavirin

- Pegasys® (PegIFN-α-2a) was *approved* to treat HCV in 2002.
- *Dose*; - Pegasys® (PegIFN-α-2a); 180 mcg SC once *weekly*, PLUS
  - Copegus® (Ribavirin); - <75 kg; 1000 mg/day. - ≥75 kg; 1200 mg/day.

Interferon alpha-2b (IFN-α-2b) + Ribavirin Oral Solution

- In 2003 Intron® A (Interferon alfa-2b) PLUS Rebetol® oral solution (Ribavirin) *approved for* treating pediatric *patients* with *chronic* HCV.

Boceprevir (Victrelis®) OR Telaprevir (Incivek®)

- In May 2011 FDA was *approved* Boceprevir and Telaprevir for used one of *them* in combination *with* PEG-Interferon PLUS Ribavirin for the *treatment* of *chronic* HCV in people with Genotype 1.
- *Dose*;
  - Boceprevir; 800 mg orally *every* 8 hrs *with* food OR Telaprevir 1,125 mg orally twice daily *with* food PLUS - PegIFN-α-2a; 180 mcg SC once *weekly*, PLUS
    - Ribavirin; - <75 kg; 1000 mg/day. - ≥75 kg; 1200 mg/day.

Simeprevir (Olysio®)#

In **May 2013 FDA** was ***approved*** **Simeprevir** (**150 mg orally once *daily* *with* food**) for used in **combination *with* PEG-Interferon PLUS Ribavirin** for the ***treatment*** of ***chronic* HCV** in people with **Genotype 1**.

Sofosbuvir (Sovaldi®)# (Mpiviropack®) (Sofolanork®) >>

In **December 2013 FDA** was ***approved*** **Sofosbuvir** [soe-FOS-bue-vir] (**400 mg orally once *daily* *with* or *without* food**) for used in **combination *with* Ribavirin *alone* OR Ribavirin PLUS PEG-Interferon-alfa** for the ***treatment*** of ***chronic* HCV** in people with **Genotype 1, 2, 3** or **4**.

Sofosbuvir NOW is used in **combination *with* Simeprevir, Ledipasvir, Daclatasvir** or **Velpatasvir *with*** or ***without* Ribavirin** {**Interferon-FREE therapy**}.

Drug Interactions; **Like *other* Protease Inhibitors (PIs)**; is ***substrates*** for **CYP3A4** *isoenzyme*

Most Common side effects; **Fatigue** and **headache**.

Cancer risk; - ***NO strong* evidence support** the **Sofosbuvir** or ***other* Direct-Acting Antiviral (DAA)** was ***linked*** with **liver cancer** (5/2018).

- **Cirrhosis** and/or **hepatitis** are ***risk factors*** for **liver cancer**.

Ledipasvir/Sofosbuvir (Harvoni®)# (Mpiviropack® Plus) (Sofolanork® Plus) >>

In **October 2014 FDA** was ***approved*** **Ledipasvir 90 mg/Sofosbuvir 400 mg, used orally *once* daily** *with* or *without* **food**.

Used *alone* OR in ***combination*** *with* **Ribavirin *in* compensated cirrhosis patients**.

Duration; **8-12 weeks (*without* cirrhosis)** or **24 weeks (*with* compensated cirrhosis)**.

Simeprevir (Olysio®)# + Sofosbuvir (Sovaldi®)#

In **November 2014 FDA** was ***approved*** **Simeprevir (Olysio®) PLUS Sofosbuvir (Sovaldi®)** in ***combination*** for the ***treatment of* HCV** in people with **Genotype 1**.

Used *alone* OR in ***combination*** *with* **Ribavirin *in* compensated cirrhosis patients**.

Duration of therapy; **12 weeks (*without* cirrhosis)** or **24 weeks (*with* compensated cirrhosis)**.

Ombitasvir/Paritaprevir/Ritonavir + Dasabuvir (Viekira Pak®)#

In **December 2014 FDA** was ***approved*** **Ombitasvir/Paritaprevir/Ritonavir (12.5mg/75mg/50mg) + Dasabuvir (250mg) (Viekira Pak®)** for the ***treatment of* HCV** in people with **Genotype 1**.

Used *alone* OR in ***combination*** *with* **Ribavirin *in* compensated cirrhosis patients**.

Duration of therapy; **12 weeks (*without* cirrhosis)** or **24 weeks (*with* compensated cirrhosis)**.

Ombitasvir/Paritaprevir/Ritonavir (Qurevo®)# (Technivie®)#

In **July 2015 FDA** was ***approved*** **Ombitasvir/Paritaprevir/Ritonavir (12.5mg/75mg/50mg)** for the ***treatment of* HCV** in people with **Genotype 4**.

Therapy; **Used *alone*** OR in ***combination*** *with* **Ribavirin *in* compensated cirrhosis patients**.

Duration of therapy; **12 weeks (*without* cirrhosis)** or **24 weeks (*with* compensated cirrhosis)**.

Daclatasvir (Daklinza®)# (Daklanork®) + Sofosbuvir (Sovaldi®)#

In **July 2015 FDA** was ***approved*** **Daclatasvir (30mg - 60mg - 90mg)** for the ***treatment of* HCV** in people with **Genotype 1 or 3** in ***combination with* Sofosbuvir (Sovaldi®)**, ***with*** or ***without* Ribavirin (*this* regimen are used in *all* genotypes)**.

Elbasvir/Grazoprevir (Zepatier®)#

- In January **2016 FDA** was ***approved*** **Elbasvir 50 mg** and **Grazoprevir 100 mg once *daily*** for the ***treatment of* HCV** in people with **Genotype 1 or 4**, **Zepatier®** was ***developed by*** **Merck**.
- ***Therapy***; **Used *alone*** OR in ***combination*** *with* **Ribavirin** if HCV RNA >800,000 IU/L.
- ***Duration of therapy***; **12 weeks** (most patient) or **16 weeks**.

Sofosbuvir/Velpatasvir (Epclusa®)#

- In June 2016 **FDA** was ***approved*** **Sofosbuvir** **400 mg** and **Velpatasvir** **100 mg once** ***daily*** for the ***treatment of*** **HCV** in people with ***all*** **genotypes**, **Epclusa®** was ***developed by*** **Gilead Sciences, Inc.**
- **Used** ***alone*** OR in ***combination*** *with* **Ribavirin** in **genotype 3** with **treatment** ***experienced***.
- ***Duration of therapy***; **12 weeks** (most patient) or **24 weeks** ***without*** **Ribavirin** in **genotype 3** with **treatment** ***experienced***.

Sofosbuvir/Velpatasvir/Voxilaprevir (Vosevi®)

- In Jul 2017 **FDA** was ***approved*** **Sofosbuvir/Velpatasvir/Voxilaprevir** **(400mg/100mg/100mg)** ***fixed-dose*** **combination** for ***treatment*** and ***re-treatment*** of **adults** with ***all*** **genotypes** of **HCV**, **Vosevi®** **(Gilead Triple Combo)** was ***developed by*** **Gilead Sciences, Inc.**
- ***Duration of therapy***; **12 weeks**.
- ***Black box warning***; ***Risk*** of **hepatitis B virus (HBV)** ***reactivation***.

Glecaprevir/Pibrentasvir (Mavyret®)

- In Aug 2017 **FDA** was ***approved*** **Glecaprevir/Pibrentasvir** **(100mg/40mg)** ***fixed-dose*** **combination** for ***treatment*** ***all*** **genotypes** of **HCV** in ***as short as*** **8 Weeks**, **Mavyret®** was ***developed by*** **AbbVie**.
- **Mavyret®** is **used** in ***all stages*** of **chronic kidney disease**.
- ***Dose***; **3 tablets** (300 mg/120 mg total dose) **orally once** ***daily*** *with* **food**.
- ***Duration of therapy***; - **8 weeks** if ***no*** **cirrhosis** and **12 weeks in cirrhosis**.
  - **16 weeks** in *some* **treatment-experienced patients** with **cirrhosis**.

Antivirals for HIV Infections (AIDS) [Antiretroviral]

A) Nucleoside/nucleotide Reverse-Transcriptase Inhibitors (NRTIs)

Reverse Transcriptase Inhibitors (**RTIs**) are a ***class*** of **Antiretroviral Drugs** used to ***treat*** **HIV infection** or **AIDS**, and in ***some cases*** **Hepatitis B**.
Nucleoside/nucleotide Reverse Transcriptase Inhibitors (**NRTIs**) are ***analogues*** of the **naturally occurring deoxynucleotides** needed to ***synthesize*** the **viral DNA** and they ***compete*** with the ***natural*** **deoxynucleotides** for ***incorporation*** into the growing **viral DNA chain**.
All **NRTIs** may be ***associated with*** **mitochondrial toxicity**, probably owing to ***inhibition*** of **mitochondrial DNA polymerase gamma**;
  * **Toxicities** *such as* **peripheral neuropathy**, **pancreatitis** & **lipoatrophy**.
  * **Dideoxynucleosides**, such as **Didanosine** and **Stavudine**, have a ***greater affinity*** for the **mitochondrial DNA polymerase**.
All **NRTIs** have been ***associated with*** a ***potentially*** **fatal liver toxicity** ***characterized by*** **lactic acidosis** and **hepatomegaly** *with* **steatosis**.

Zidovudine (ZDV) (Retrovir®)#

Zidovudine is the ***first drug*** approved by **FDA** for **HIV**; is a ***thymidine analog***.
It is **used** in ***treatment of*** **HIV** in **children** and **adults** and to ***prevent*** **perinatal transmission** of **HIV**, it is also **used** for ***prophylaxis***.
Common side effects; **Anemia**, **Neutropenia**, **Headache** and **GI intolerance**.

Stavudine (d4T) (Zerit®)#

Stavudine is a ***thymidine analog***.
Side effects and toxicity; **Headache**, **GI intolerance**, and **Peripheral Neuropathy**, **Pancreatitis**, **Lactic Acidosis** and **Hepatomegaly** *with* **Steatosis**.

Didanosine (ddI) (Videx®)#

Didanosine is the ***second drug*** approved by the **FDA** for the *treatment of* **HIV**.
Toxicity; ***Dose-dependent*** **Pancreatitis**, **Lactic Acidosis** and **Hepatomegaly** *with* **Steatosis**.
Side effects; **Peripheral Neuropathy** and **Diarrhea**.

Abacavir (ABC) (Ziagen®)#

Abacavir is a *guanosine analog*.
Abacavir *should be* used in combination in HIV Infection with *other* antiretroviral agents, Abacavir is *available* in a *fixed-dose combination formulation*;
- Kivexa®; Abacavir/Lamivudine.
- Triumeq®; Abacavir/Dolutegravir/Lamivudine.
- Trizivir®; Abacavir/Lamivudine/Zidovudine.

Serious side effects; hypersensitivity reaction.
Cautions; Abacavir *should be* used *cautiously* in patients with *existing* cardiac *risk factors* due to a possible *increased* risk *of* myocardial *events*.

Lamivudine (3TC) (Zeffix®)#

Lamivudine is *typically* used in combination with *other* Antiretrovirals like Zidovudine and Abacavir.
Serious side effects; Lactic acidosis and hepatomegaly.

Emtricitabine (FTC) (Emtriva®)

Emtricitabine is a *fluoro derivative* of Lamivudine, *inhibits both* HIV and HBV RT.
- Emtricitabine is used in combination, *typically with* Tenofovir and *other* Antiretrovirals, *like*; *Integrase Inhibitors* and others;
  - Truvada®; Emtricitabine/Tenofovir.
  - Atripla®; Emtricitabine/Tenofovir/Efavirenz.
  - Complera®, Eviplera®; Emtricitabine/Tenofovir/Rilpivirine.
  - Stribild®; Emtricitabine/Tenofovir/Elvitegravir/Cobicistat.

Toxicity; Hyperpigmentation, lactic acidosis and hepatomegaly.

Tenofovir Disoproxil Fumarate (TDF) (Viread®)

Tenofovir Alafenamide (TAF) (Vemlidy®)

Tenofovir is adenosine *analog* used in HIV Infection and chronic hepatitis B.
Tenofovir is used in *combination*, with Emtricitabine and Efavirenz;
- Truvada®; Emtricitabine/Tenofovir.
- Atripla®; Efavirenz/Emtricitabine/Tenofovir.

Zalcitabine (ddC) (Hivid®)

- Zalcitabine or 2′-3′-dideoxycytidine (ddC) is a *cytosine analog* and it was the *third* antiretroviral to be approved by the FDA for the *treatment of* HIV/AIDS.
- Zalcitabine has even been *removed from* some countries and *less* used today.

B) Non-nucleoside Reverse-Transcriptase Inhibitors (NNRTIs)

Non-nucleoside Reverse-Transcriptase Inhibitors (NNRTIs) bind *directly* at an allosteric hydrophobic site *adjacent* to the active site, inducing a *conformational* change that *results* in enzyme inhibition and *block* viral dependent DNA polymerase *activity*.
All NNRTIs have been *associated with* hypersensitivity reactions, *including* rash.

Efavirenz (EFV) (Sustiva®)#

Efavirenz is the *preferred* NNRTIs, *widely* used to *treat* and *prevent* HIV/AIDS in *combination* with *other* antiretrovirals; Atripla®; Efavirenz/Emtricitabine/Tenofovir.
Should be taken on an *empty stomach* (*to reduce CNS side effects*).
Efavirenz is a *substrate of* the CYP450;
- *Inhibits*: CYP2C9, CYP2C19, and CYP3A4 (*in vitro*).
- *Induces*: CYP3A4 (*in vivo*).

Most common side effects; CNS side effects (dizziness, headache, vivid dreams, loss *of* concentration and depression) and skin rash.
Other common side effects; Nausea, vomiting, diarrhea & *increase* total serum cholesterol.

Nevirapine (NVP) (Viramune®)#

Nevirapine is used in *combination with* other antiretroviral drugs for the *treatment* of HIV.
Black Box Warning; Skin reactions, Hepatotoxicity and Monitoring.
- *Severe*, *life-threatening* skin reactions; *including* Stevens-Johnson syndrome and toxic epidermal necrolysis.
- *Severe*, *life-threatening*, and in *some cases* *fatal* hepatotoxicity.

Monitoring; *during* the *first* 18 weeks of therapy *essential*; *extra* vigilance warranted *during first* 6 weeks of therapy (period of greatest risk).

Delavirdine (DLV) (Rescriptor®)#

- Delavirdine is *currently* *rarely* used.

Etravirine (ETR) (Intelence®)#

Etravirine is a *second-generation* NNRTI *active against many* HIV strains that are *resistant* to the *first-generation* NNRTIs; *approved in* 2008.
Most common side effects; Rash, Nausea and *Increased* LDL.

Rilpivirine (RPV) (Edurant®)#

Rilpivirine is a *second-generation* NNRTI; *approved in* 2011.
Rilpivirine is *approved for* HIV treatment-naïve patients in *combination with* other antiretroviral agents. It taken *orally* with meals and has pH-dependent *absorption* (avoid co-administered with acid suppression therapy and antacids and requires dose separation).
Odefsey®; A *newer* fixed-dose *combination* was *approved* in 2016; Rilpivirine/Emtricitabine/Tenofovir Alafenamide.
Most common side effects; Depression, headache, drowsiness and rash.

C) Protease Inhibitors (PIs)

Common side effects of PIs; Nausea, vomiting, diarrhea and *disturbances* in glucose and lipid metabolism (*diabetes, hypertriglyceridemia and hypercholesterolemia*) and fat redistribution (*buffalo hump* and breast enlargement).
Drug interactions; PIs are *substrates* and *potent inhibitors* of CYP450.
- *For example* *dangerous* interactions *with* PIs *include*;
  - Rhabdomyolysis from Simvastatin or Lovastatin.
  - Excessive sedation from Midazolam or Triazolam.
  - Respiratory depression from Fentanyl.

Ritonavir (RTV) (Norvir®)#

Ritonavir is *widely* used *as* a Pharmacokinetic Enhancer or "*booster*" of *other* PIs.
Mechanism; Ritonavir is a *potent* inhibitor of CYP3A, and *concomitant* Ritonavir *administration* at *low* doses *increases* the *bioavailability* of the *second* PI, often *allowing for* *longer* dosing intervals; - Kaletra®; Lopinavir/Ritonavir; in HIV/AIDS.
- Qurevo®; Ombitasvir/Paritaprevir/Ritonavir; in hepatitis C.

Saquinavir (SQV) (Invirase®)#

Saquinavir is *typically* used with Ritonavir or Lopinavir/Ritonavir.
Absorption; *poor*; *increased* with *high* fat meal.
Saquinavir may be *associated with* QT and PR interval *prolongation* (ECG *should be* done *prior to* *starting* therapy).

Indinavir (IDV) (Crixivan®)#

Indinavir has a *poor* pharmacokinetic profile, so it is *now rarely* used; *Shortest* half-life and *latest* protein bound of *all* PIs.
Indinavir *characteristically* causes Nephrolithiasis/Urolithiasis and Hyperbilirubinemia.
Precautions; *Adequate* hydration (at least 1.5 L of water per day) is important to *reduce* the incidence of kidney stone formation.

Nelfinavir (NFV) (Viracept®)#

Nelfinavir ***should be*** **taken** ***with*** **food** (bioavailability increased 2.5 to 5 times).
Nelfinavir is the ***only*** **PI** that ***cannot*** be **boosted** by **Ritonavir** (not extensively metabolized by CYP3A).
Nelfinavir ***characteristically*** causes **Diarrhea**; **Food** also ***decreases*** the **risk** of **diarrhea**.
Nelfinavir ***off-label used*** in **Multiple Myeloma**.

Amprenavir (Agenerase®)# | **Fosamprenavir (FPV)** (Lexiva®)# (Telzir®)#

Fosamprenavir is a ***prodrug*** that is *metabolized to* **Amprenavir**.
Fosamprenavir is **used** in ***combination***, ***typically*** with ***low-dose*** **Ritonavir** or ***other*** **antiviral drugs**.
- ***Most common side effects***; **Nausea**, **diarrhea**, **fatigue** and **rash**.

Lopinavir/Ritonavir (LPV/r) (Kaletra®)#

Lopinavir *available as* a ***fixed-dose*** **combination** **Lopinavir/Ritonavir** (*booster*).

Atazanavir (ATV) (Reyataz®)# | **Tipranavir (TPV)** (Aptivus®)#

Darunavir (DRV) (Prezista®)#

This agents are ***second*** **generation PIs**; ***preferred PIs***.
Atazanavir ***inhibits*** **glucuronyl transferase**; cause **hyperbilirubinemia** & **jaundice**.
Tipranavir ***rarely*** cause **fatal hepatitis** and **intracranial hemorrhage**.

D) Entry (Fusion) Inhibitors

Enfuvirtide (Fuzeon®)# | **Maraviroc** (Selzentry®)#

Enfuvirtide *available as* ***injectable form***, while **Maraviroc** *available as* ***oral tablets***.
Maraviroc has ***black box warning*** for **hepatotoxicity**.

E) Integrase Strand Transfer Inhibitors (INSTIs)

Raltegravir (RAL) (Isentress®)# | **Elvitegravir (EVG)** (Vitekta®)#

Dolutegravir (DTG) (Tivicay®)#

Integrase Strand Transfer Inhibitors (**INSTIs**), *often called* **Integrase Inhibitors** (**INIs**), *work by* ***inhibiting*** the **insertion** of **viral DNA** ***into*** the **host cell DNA**.
They are **used** as part of the ***combination*** **therapy**.
Most common side effects; **Nausea** and **diarrhea**.

Common Fixed Dose Combination Brands

Truvada®; **Emtricitabine/Tenofovir**.
Kaletra®; **Lopinavir/Ritonavir**.
Kivexa®; **Abacavir/Lamivudine**.
Dutrebis®; **Lamivudine/Raltegravir**.
Evotaz®; **Atazanavir/Cobicistat**.
Prezcobix®; **Darunavir/Cobicistat**.
Combivir®; **Lamivudine/Zidovudine**.
Trizivir®; **Abacavir/Lamivudine/Zidovudine**.
Triumeq®; **Abacavir/Dolutegravir/Lamivudine**.
Odefsey®; **Rilpivirine/Emtricitabine/Tenofovir Alafenamide**.
Genvoya®; **Elvitegravir-Cobicistat/Emtricitabine/Tenofovir Alafenamide**.
Atripla®; **Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate**.
Complera®, **Eviplera®**; **Emtricitabine/Rilpivirine/Tenofovir Disoproxil Fumarate**.
Stribild®; **Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate**.

Antiparasitic Drugs

Anthelmintic Drugs

Anti-Nematodes (Round Worm)

- *Most common* **Nematodes**;
  - **Hookworms**; *Ancylostoma duodenale*.
  - **Pinworms**; *Enterobius vermicularis*; **Oxyuris**.
  - **Threadworms**; *Strongyloides stercoralis*.
  - **Roundworms**; *Ascaris lumbricoides*.
  - **Whipworms**; *Trichuris trichiura*.
  - **Tissue Nematode**; as *Loa loa* (**Filariasis**).

Mebendazole (Vermox®)# (Antiver®) | Flubendazole (Fluvermal®)# (Verm-All®)#

Mebendazole is a ***synthetic*** **benzimidazole**, a ***broad-spectrum*** **antihelminthic agent**.

Mebendazole is a ***first-line*** **agent** for the **treatment** *of* ***many types*** *of* **Nematodes** such as; **pinworm** and **hookworm infections**, **ascariasis**, **trichuriasis** and **strongyloidiasis**.

Mebendazole is an ***alternative*** to **Metronidazole** in **Giardiasis**;

** **Stevens–Johnson syndrome** and the ***more severe*** **toxic epidermal necrolysis** can occur when **Mebendazole** is ***combined with*** high ***doses*** of **Metronidazole**.

Benzimidazoles are ***kills*** **hookworm**, **Ascaris**, and ***Trichuris*** **eggs**; ***not need*** **dose** ***repeated***.

Absorption; *less than* **10%** of **orally** ***administered*** **Mebendazole** is **absorbed**; **absorption** is ***increased*** with a **fatty meal**.

Dose; - **Hookworm infections**, **Ascariasis** & **Whipworm** (**trichuriasis**); ≥ 2 years; **100 mg orally** ***every*** **12 hours** *for* **3 days**, *If cure* is not achieved 3 weeks after treatment, a 2nd course of treatment is advised.

- **Pinworm** (***Enterobius vermicularis*** = **Oxyuriasis**; ***Oxyuris***); ≥ 2 years; **100 mg** orally **once** as a ***single dose***; this dose ***should be*** repeated in **2 weeks**.
- **Giardiasis**; **200 mg orally** ***every*** **8 hours** *for* **5 days**; as ***alternative*** to **Metronidazole**.

* **Mebendazole 500 mg** (**Verm-1®**); can be given as a ***single*** **dose**.

Side Effects; - ***Common***; **Diarrhea** and **abdominal pain**

- ***High-dose***; **hypersensitivity reactions** (rash, urticaria), **agranulocytosis**, **alopecia** and ***elevated*** **liver enzymes**.

Pregnancy; **US FDA pregnancy category C** (Animal studies have revealed evidence of fetotoxicity and teratogenicity) ***only*** **recommended** for use ***during*** **pregnancy** when **benefit** ***outweighs*** **risk**.

Pyrantel Pamoate (Pin-X®)

- **Pyrantel pamoate** is a ***broad-spectrum*** **antihelminthic** ***highly*** **effective** for the *treatment of* **Pinworm**, **Hookworm**, **Ascaris** and **Trichostrongylosis**.
- ***Dose***; 11 mg/kg base (maximum 1 g) orally **once** (Hookworm a **3-day** course); repeat dose in 2 weeks.
- ***Common Side Effects***; **Nausea**, **vomiting** and **diarrhea**.

Ivermectin (Iverzine®) (Ivermine®)

Ivermectin is the ***drug of choice*** for the **treatment** of; **Cutaneous Larva Migrans**, **Strongyloidiasis**, and **Onchocerciasis** (**river blindness**) caused by ***Onchocerca volvulus***.

It is ***highly effective*** ***against*** **Head lice**, **Scabies** and **Lymphatic Filariasis**, ***among*** **others**.

Albendazole–Ivermectin Combination Therapy; used in **Filariasis**.

- ***Usual Doses***; - **Onchocerciasis** (**river blindness**); 0.15 mg/kg orally once every 3-12 months.
- **Strongyloidiasis**; 0.2 mg/kg orally once.

Side Effects; - **Onchocerciasis**; **Mazzotti Reaction**; **fever**, **headache**, **dizziness**, **somnolence** and **hypotension**; **severity** ***related to*** **parasite load**; **Antihistamines** or/and **Corticosteroids** may be ***given*** to ***decrease*** the **symptoms**.

-**Strongyloidiasis**; **Fatigue**, **dizziness**, **nausea**, **vomiting**, **abdominal pain** & **rashe**

Diethylcarbamazine (Hetrazan®)

- **Diethylcarbamazine** is the ***drug of choice*** for **Filariasis**; ***including*** **Lymphatic Filariasis** (**Elephantiasis**; ***Wuchereria bancrofti***, ***Brugia malayi*** and ***Brugia timori***), **Loiasis** (***Loa loa***) and **Tropical Pulmonary Eosinophilia** (***Wuchereria bancrofti***).
- **Diethylcarbamazine** is ***commonly*** **used** in ***combination*** with **Albendazole** in **Filariasis**.
- ***Usual Adult Dose***; - Day 1: 50 mg orally.
  - Day 2: 50 mg three times daily
  - Day 3: 100 mg three times daily
  - Day 4-14: 6 mg/kg/day divided into three times daily*.

  * In *Loa Loa*; Day 4-21: 9 mg/kg/day divided into three times daily.
- **Antihistamines** or/and **Corticosteroids** may be ***given*** to ***decrease*** **severe reactions** (*due to* release of proteins from dying microfilariae).
- ***Common Side Effects***; **Fever, nausea, vomiting, arthralgia** and **headache**.

Levamisole (Ergamisol®) (Katrex®)#

- **Levamisole** is an ***anthelmintic/immunomodulator drug***, used as ***alternative*** for the **treatment** of **Ascariasis** and **Hookworm infections**.

Anti-Cestodes (Tapeworms)

- ***Most common*** **Cestodes**;
  - **Fish worm**; ***Diphyllobothrium latum***.
  - **Pork tapeworm**; ***Taenia solium***.
  - **Rat tapeworm**; ***Hymenolepis diminuta***.
  - **Beef tapeworm**; ***Taenia saginata***.
  - **Dwarf tapeworm**; ***Hymenolepis nana***.
  - **Tissue Cestoda**; **Hydatidosis**.

Niclosamide (Yomesan®)# (Niclosan®)

- **Niclosamide** **now** is a ***second-line*** **drug** (*alternative to* **Praziquantel**) for the *treatment* of ***most*** **Cestode infections**, ***no longer*** **available** in **USA** ***according to*** **CDC** *recommendations* (***using*** **Praziquantel**; as **single dose**).
- **Niclosamide** ***rapidly*** **kill adult worms** (*but* ***not*** **ova**) by *causing* **necrosis** of the **head** and **adjoining segments** of the **tapeworm**.
- ***Dose***; **500 mg Chewable Tablet** (*in* **foil cover**);
  - **Beef tapeworm** (***Taenia saginata***), **Pork tapeworm** (***Taenia solium***) and **Fish tapeworm** (***Diphyllobothrium latum***); **One *single* dose** is ***sufficient***;
    - < 2 years; 1 tablet (500 mg)
    - 2-6 years; 2 tablets
    - >6 years; 4 tablets
  - **Dwarf tapeworm** (***Hymenolepis nana***);
    - 7 **days** is *recommended*; **Praziquantel** is ***superior***;
      - **First day**: - < 2 years; 1 tablet (500 mg) - 2-6 years; 2 tablets - >6 years; 4 tablets
      - *Another* **six days**: - < 2 years; 1/2 tablet - 2-6 years; 1 tablets - >6 years; 2 tablets

PATIENT COUNSELLING # # # # # # #

1) ***Don't*** **remove** ***from*** **foil** ***until*** *immediately* ***before*** **administration**.
2) **Tablets** ***should be administered*** in the **morning** on an ***empty*** **stomach**.
3) **Tablets** ***should be*** **chewed** *before* **swallowing** and **washed down** with a ***little*** **water**.
4) **Patients** ***should*** receive a **saline purgative** (e.g. **Sodium sulfate**, **Magnesium sulfate**) **2 hours** ***after*** the **Yomesan®**; to **ensure** a ***rapid*** and ***complete*** **expulsion** of the **worm**.
5) **Alcohol** ***should be*** **avoided** ***within*** **1 day** of **Niclosamide** ***use***.

- **Niclosamide** may be given ***safely*** in **pregnancy** (**Category B**) and to **patients** ***with*** **liver**, **biliary** and **kidney** ***diseases***.
- ***Common Side Effects***; ***Mild*** **GI disturbances** (Nausea, vomiting, diarrhea & abdominal discomfort).

Albendazole (Zentel®)# (Alzental®) (Bendax®)

- **Albendazole**, is a **broad-spectrum** ***benzimidazole*** **antihelminthic** (**Benzimidazole Carbamate**) **effective** ***against*** ***many*** ***types*** *including*; **Cestodes** and **Nematodes**.

It is the ***drug of choice*** of **Hydatid Disease** and **Cysticercosis** (**Tissue Cestodes**).

It is ***also*** **used** in the *treatment of* ***many*** ***types*** *of* **Nematodes** such as; **Pinworm** and **Hookworm infections**, **Ascariasis**, **Trichuriasis** and **Strongyloidiasis**.

Albendazole is an ***alternative*** or ***adjunct*** to **Metronidazole** in **Giardiasis** ***especially*** *in* **children**.

Albendazole also has **larvicidal** ***effects*** in **Hydatid Disease**, **Cysticercosis**, **Ascariasis** and **Hookworm infection** and **ovicidal** ***effects*** in **Ascariasis**, **Ancylostomiasis** and **Trichuriasis**.

Albendazole is **used** in ***combination*** with **Diethylcarbamazine** or **Ivermectin** in **Filariasis**.

- ***Absorption***; ***Erratically*** **absorbed** *after* **oral administration**, *but* **absorption** is ***enhanced*** by a ***high*-fat meal** (***up to*** **4-5 times**).

Doses; - **Neurocysticercosis** (***Taenia Solium*** **Cyst** in the **brain**);
  - >60 kg: 400 mg orally twice daily with meals for 8-30 days.
  - <60 kg: 15 mg/kg/day orally in divided doses twice a day with meals for 8-30 days (Max.800 mg/day).
- **Hydatid Disease**;
  - >60 kg: 400 mg orally twice daily with meals for 28 days, THEN 14 drug-free days for 3 cycles.
  - <60 kg: 15 mg/kg/day orally in divided doses twice a day with meals for 28 days, THEN 14 drug-free days x 3 cycles (Max.800 mg/day).
- **Ancylostoma**, **Ascariasis**, **Hookworm**, **Trichostrongylus**; 400 mg orally once.
- **Pinworm**; 400 mg orally once, repeat in 2 weeks.

Common Side Effects; ***Mild*** and ***transient***; **Headache** and **nausea**.

Long term therapy (**Hydatid Disease**; **3 months**); ***risk*** of **hepatotoxicity** and, *rarely*, **agranulocytosis** or **pancytopenia** (drop in white blood cells, red blood cells and platelets).

Pregnancy; **US FDA category C** and **category D** in **Australia**; ***only*** **recommended** for use ***during*** **pregnancy** when **benefit** ***outweighs*** **risk**.

Anti-Trematodes (Flukes) (Flatworms) (Leaf-shaped)

- ***Most common*** **Trematodes**;
  - **Intestinal flukes**; ***Heterophyes heterophyes*** (**Heterophyiasis**).
  - **Liver flukes**; ***Fasciola*** (**Fascioliasis**).
  - **Lung flukes**; ***Paragonimus*** (**Paragonimiasis**).
  - **Blood flukes**; ***Schistosoma*** (**Schistosomiasis**).

Praziquantel (Biltricide®)# (Distocide®)

Praziquantel is a ***drug of choice*** for the treatment of ***all forms*** of **Schistosomiasis**, other **Trematode Infections** and **Cestode Infections** ***such as*** **Taeniasis** *including* **Cysticercosis**.

The **drug's** **safety** and **effectiveness** as a ***single*** **oral dose** have also ***made*** it **useful** in mass ***treatment of*** **several infections**.

Praziquantel acts by ***increase*** **cell membrane** ***permeability*** to **Calcium**, *causing* **contracture** and **paralysis** of the **parasite**.

Praziquantel ***should be*** **taken** *with* **food** (**not chewed** *due to* a **bitter taste**).

Doses; - **Schistosomiasis**; 20 mg/kg/dose orally in 3 doses (4-6 hrs) for 1 day.
- **Clonorchiasis**, **Opisthorchiasis** & **Paragonimiasis**; 25 mg/kg/dose 3 times daily for 2 days
- **Taeniasis** and **Diphyllobothriasis**; 5-10 mg/kg orally once (nearly 100% cure rates).
- **Tapeworms**; 5-10 mg/kg as ***single dose*** or 25 mg/kg if ***Hymenolepis nana***.

Common Side Effects; **Dizziness**, **malaise**, **headache** and **GIT disturbance**.

Contraindications; **Praziquantel** is ***contraindicated*** for the **treatment** of **Ocular Cysticercosis**, ***because*** **destruction** of the **organism** in the **eye** may cause ***irreversible*** **damage**.

Antiprotozoal Drugs (most common only)

- *Most common* **Protozoa**;
  - *Plasmodium*; **Malaria**.
  - *Giardia lamblia*; **Giardiasis**.
  - *Leishmania*; **leishmaniasis**.
  - *Entamoeba histolytica*; **Amoebiasis**.
  - *Trichomonas vaginalis*; **Trichomoniasis**.
  - *Toxoplasma Gondii*; **Toxoplasmosis**.
  - **African sleeping sickness**.

for Amoebiasis (Amebicides)

Metronidazole (Flagyl®)# (Amrizole®)

Metronidazole is a ***nitroimidazole***, is the ***mixed*** **amebicide *of choice*** for ***treating*** **amebic infections** (***kills*** **Trophozoites** but ***not*** **Cysts**).

Uses:- **Giardiasis** (*Giardia lamblia*) and **Trichomoniasis** (*Trichomonas vaginalis*).
- **Infections *caused by* *anaerobic* cocci**, and ***anaerobic*** **gram-negative bacilli**.
- ***Helicobacter pylori***-associated **peptic ulcer disease**.
- ***Drug of choice*** for the *treatment of* **bacterial vaginosis**.
- ***Drug of choice*** for the *treatment of* **pseudomembranous colitis** caused by ***C. difficile***.

Dose for **Amebiasis**; - ***Adult***; 500-750 mg orally every 8 hours for 5-10 days.
- ***Children***; 35-50 mg/kg/day orally/IV divided every 8 hours for 10 days.

N.B.; To ***kill*** **cysts *confined*** to the **intestine**; **Iodoquinol**, **Paromomycin** and **Diloxanide**; **One** of ***these drugs*** may **use *along with*** **Metronidazole**; **Furazol®**; **Metronidazole + Diloxanide**.

Side Effects;
- ***Unpleasant*** **metallic taste**.
- **Nausea**, **vomiting** and **abdominal pain**.
- **Disulfiram-*like reaction***; Occur when **Metronidazole** ***ingested with*** **Alcohol** cause ***severe*** **flushing**, **tachycardia** and **hypotension** (**Disulfiram-*like reaction***).
- **Metronidazole *alone rarely*** *causes* **Stevens–Johnson syndrome**, ***but*** is reported to occur at ***high rates*** when ***combined with*** **Mebendazole**.
- ***Infrequent*** **side effects**; **diarrhea**, **insomnia**, **weakness**, **dizziness**, **thrush**, **rash**, **dysuria**, **dark urine**, **vertigo**, **paresthesia** and **neutropenia**.

Pregnancy and ***Lactation***;
- ***Pregnancy***; **FDA Category B** (***No evidence*** of **harm** to the **fetus** *due to* **Metronidazole**).
- ***Lactation***; ***excreted in*** **human milk**; ***Not*** **recommended** (**Concentration** in the **milk** ***similar to*** **maternal serum** ***levels***).

- ***Warning***; **Metronidazole** *has been shown* to be **carcinogenic** in **mice** and **rats**.

Tinidazole (Fasigyn®)# | Secnidazole (Flagentyl®)# | Ornidazole (Ornidaz®)

- **Tinidazole**, **Secnidazole** and **Ornidazole** are ***nitroimidazole***, ***similar to*** **Metronidazole** in **spectrum** of **activity**, **absorption**, **adverse effects** and **drug interactions**.

Dose;
- **Tinidazole** (**Amebiasis**); 2 g (4 tab. 500 mg) orally once with food for 3 days (intestinal), 3-5 days (liver)
- **Secnidazole** (**Bacterial Vaginosis**); 2 g (4 tab. 500 mg) orally once.

Iodoquinol (Yodoxin®) | Paromomycin (Humatin®) | Diloxanide (Amoebyl®)

- They are **luminal amebicide** (**Asymptomatic Amebiasis**) and **commonly** ***used with*** **Metronidazole**.

Chloroquine (Aralen®)# (Resochin®)#

Chloroquine is an ***antimalarial agent***, it is also ***used for*** **amebiasis** (*combination with* **metronidazole**) in **amoebic liver abscesses**, **rheumatoid arthritis** & **lupus erythematosus**.

Side Effects; - **GI upset**, **pruritus** and **headaches**.
- **Blurred vision** (**Chloroquine retinopathy**);
  - Ophthalmologic examination ***should be*** *routinely* performed.
- **QT interval prolongation** *may occur*.

Chloroquine *may be* ***associated*** **hemolytic anemia** in **patients** *with* **glucose-6-phosphate dehydrogenase** ***deficiency***.

for Malaria (Antimalarial Drugs)

Quinine and Quinidine

Quinine and Quinidine are used in falciparum malaria; *especially* severe disease.
Side Effects;
  # Cinchonism Syndrome; **Tinnitus, headache, nausea, dizziness, flushing,** and **visual disturbances** (*reversible*); Not reasons for suspending therapy.
  # Hemolytic anemia (*especially* in **G6PD *deficiency***), Thrombocytopenia & **Leukopenia**; Quinine therapy ***should be*** suspended.
  # Hypersensitivity reactions; **rashes, angioedema** & **bronchospasm**.
  # It ***must*** be **used** with ***great* caution** in **patients** with **cardiac abnormalities**.

Primaquine

Primaquine is the ***drug of choice*** for the ***eradication*** of **dormant liver forms** of ***P. vivax*** and ***P. ovale*** and *can also* be **used** *in* **chemoprophylaxis** for ***all*** **malarial** ***species***.
Primaquine is *associated with* ***drug-induced* hemolytic anemia** in ***patients with*** **glucose-6-phosphate dehydrogenase (G6PD) deficiency**.

Mefloquine (Lariam®)#

Mefloquine is **one** of the *recommended* **chemoprophylactic drugs** for use in ***most*** **malaria-endemic regions** *with* **Chloroquine-*resistant* strains** (**Chloroquine- *resistant P. falciparum***).
Long half-life (**20 days**) (**enterohepatic *circulation*, *highly*** protein-bound and ***extensively*** concentration in **tissues**); ***allowing* BEST *weekly* dosing** for **chemoprophylaxis**.
Dose;
- **Acute Malaria Infections**; **1250 mg orally *once*** as a **single dose**.
- **Malaria Prevention**; **250 mg orally *once*** **weekly** on the ***same*** **day** of ***each*** **week**;
  1-2 *week* before >> during >>> 4 *weeks* after
  - ***Start* 1-2 weeks *before*** **arrival** in **endemic area**.
  - ***Continue*** *every* **week *during*** **staying** in **endemic area**.
  - ***Continue* 4 weeks *after*** **leaving endemic area**.

Most common; **nausea, vomiting** and **dizziness**.
- **FDA Warning**; * **Neuropsychiatric side effects**; **Depression, hallucinations** and **anxiety**.
  * **Neurological side effects**; ***Poor* balance, seizures** and **tinnitus**.
- **Mefloquine** *may cause* ***abnormalities*** with **heart rhythms**.

Artemisinin or Qinghaosu

- **Artemisinin** ***its* derivatives** are ***recommended* first-line agents** for the *treatment of* ***multidrug-resistant P. falciparum* malaria**.
- *Currently* **Artemisinin-*based* *combination* *therapy*** (**ACT**) and ***recommendations***;
  R; WHO Guidelines for the treatment of malaria. 3rd edition, April 2015
  - *For* ***uncomplicated* falciparum malaria** (Adult and children, EXCEPT pregnant in 1st trimester); **ACT regimens *should* provide 3 days'** treatment with an Artemisinin derivative
    - **Artemether + Lumefantrine (Coartem®)**
    - **Artesunate + Amodiaquine (Camoquin®)**
    - **Artesunate + Mefloquine (Artequin®)**
    - **Artesunate + Sulfadoxine/Pyrimethamine (SP)**
    - **Dihydroartemisinin + Piperaquine (Duo-Cotecxin®)**
    * **Pregnant** in **1st *trimester***; **Quinine + Clindamycin** *for* 7 days.
    * If the **malaria species** is ***not known*** with certainty, ***treat as*** for **uncomplicated *P. falciparum*** **malaria**.
  - *For* ***severe* malaria**;
    - **IV** or **IM Artesunate** for *at least* **24 hours** and ***until*** they *can* ***tolerate* oral medication, once** a **patient** has ***received* *at least* 24 hours** of ***parenteral* therapy** and ***can* tolerate oral therapy, *complete* treatment** *with* **3 days** of **ACT**.

Side Effects;

- **Artemisinins** are ***generally*** ***very well*** **tolerated**.
- ***Most commonly*** *reported*; **Nausea**, **vomiting**, **anorexia** and **dizziness**.
- ***High doses*** may cause **QT interval** ***prolongation***.
- **Hypersensitivity** ***reactions*** and **rash** *may* **occur**.

Pyrimethamine + Sulfadoxine (Fansidar®)#

- **Pyrimethamine/Sulfadoxine** are typically *given* with **Folinic acid** (**Leucovorin**; to reduce side effects related to folate deficiency in the patient).
- **Pyrimethamine/Sulfadoxine** **now** ***used*** in ***combination*** with **Artesunate** for the ***treatment*** of ***uncomplicated P. falciparum*** **malaria**.
- **Pyrimethamine** is also **used** in ***combination*** with **Sulfadiazine** to treat ***active*** **toxoplasmosis**.
- **Pyrimethamine** is also **used** *with* **Dapsone** as a ***second line*** option to **prevent** ***Pneumocystis jiroveci*** **pneumonia** (**PCP**) in **people** *with* **HIV/AIDS**.

Chloroguanide (Proguanil)/Atovaquone (Malarone®)

- **Atovaquone/Proguanil** is ***fixed*** **dose** ***combination*** *approved for* **both** ***treatment*** and ***prophylaxis*** of **malaria** in **chloroquine-resistant areas**.

Precautions;

* In ***event of*** **vomiting** *within* **1 hour** of **dose**, ***repeat*** **dose**.

* It ***should be*** **taken** *with* **food** or **milk** to ***enhance*** **absorption**.

for Leishmaniasis

Sodium Stibogluconate (Pentostam®) | Meglumine Antimoniate (Glucantim®)

- They are ***injectable*** ***Pentavalent*** **Antimonial Agents** *generally* **considered** ***first-line*** **agents** for **cutaneous** and **visceral leishmaniasis**.

Miltefosine (Impavido®)

- **Miltefosine** is the ***first*** **orally** **active drug** for **visceral leishmaniasis**.
- **Pregnancy** and **Black Box Warning**; **US FDA pregnancy category D**; ***Adequate*** **methods** of **contraception** *should be* **advised** ***during*** **therapy** and for **5 months** ***after*** **therapy**.

➢ Dosage of Commonly Antimicrobial in Children:-

Amoxicillin or **Ampicillin**; 25–50 mg/kg/day
Ampicillin/Sulbactam; 300 mg/kg/day
Amoxicillin/Clavulanic; 20–90 mg/kg/day
Piperacillin/Tazobactam; 80-100 mg/kg/4-6 hrs
Cephalexin; 25–50 mg/kg/day
Cefadroxil; 30 mg/kg/day
Cephradine; 25–50 mg/kg/day
Cefaclor; 20–40 mg/kg/day
Cefuroxime; 30 mg/kg/day
Cefprozil; 15–30 mg/kg/day
Ceftriaxone; 50–75 mg/kg/day
Cefotaxime; 50–200 mg/kg/day
Ceftazidime; 30–50 mg/kg/8 hours
Cefixime; 8 mg/kg/day
Cefdinir; 14 mg/kg/day
Cefpodoxime; 10/kg/day
Linezolid; 10 mg/kg/8 hours
Erythromycin; 40–50 mg/kg/day
Clarithromycin; 15 mg/kg/day

Azithromycin; 10 mg/kg/day
Clindamycin; 8–20 mg/kg/day
Sulfamethoxazole; 8-10 mg **TMP**/kg/day
Fluconazole; 3–12 mg/kg/day
Nystatin; 1-12 months; 200,000 units/dose
1-18 years; 400,000-600,000 units/dose
Griseofulvin; Micro; 10-20 mg/kg/day
Ultra; 5-15 mg/kg/day
Acyclovir; 10–20 mg/kg/dose
Amantadine; 5–10 mg/kg/day
Lamivudine; 3 mg/kg/day
Mebendazole; 200 mg/day; all ages
Flubendazole; 200 mg/day; all ages
Albendazole; 400 mg/day; all ages
Chloroquine; 8 mg/kg/dose
Mefloquine; 20–25 mg/kg/dose
Metronidazole; 35–50 mg/kg/day
Tinidazole; 50 mg/kg/day

Gastrointestinal Tract (GIT)

Subject	No. of page
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Drugs for Irritable Bowel Syndrome (IBS)	75
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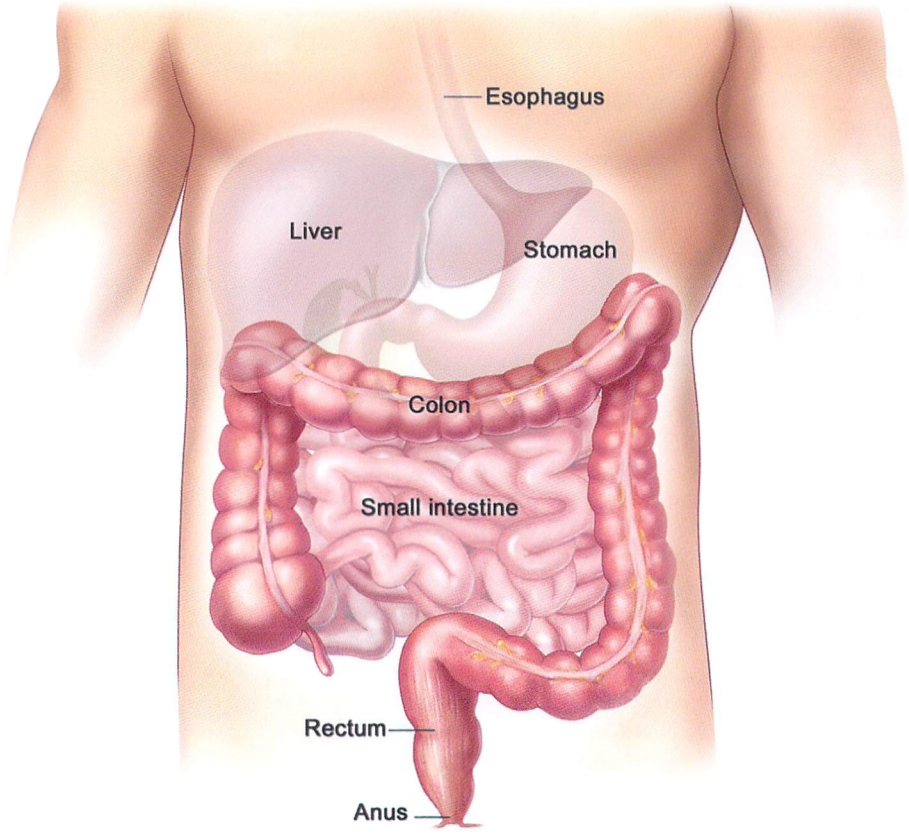
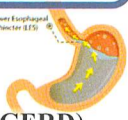


Drugs for Peptic Ulcer Disease (PUD)



- **Peptic Ulcer Disease** (**PUD**) ***or*** **Peptic Ulcer**, is a ***break in*** *the* ***lining of***;
  - * **Stomach** (**gastric ulcer**), ***or***
  - * *First part of* **small intestine** (**duodenal ulcer**), ***or***
  - * *Lower* **oesophagus**; *results from* ***chronic*** **gastroesophageal reflux disease** (**GERD**)
- ***Most common symptom*** *of* **PUD** is **epigastric pain**, *classically*, ***shortly*** **after meals** *with* **gastric ulcer** and **1-3 hours after meals** *with* **duodenal ulcer**.
- ***Symptoms of hyperacidity***; **heart burn**, **gases**, **indigestion** and **regurgitation**.
- ***Most common causes*** *of* **PUD** are ***Helicobacter pylori*** (***H. pylori***) **infection** and **NSAIDs**.

Lifestyle Modifications

- ***Lifestyle Modifications***; **GERD**, **PUD**, and **Hyperacidity**
  - **A) Dietary modifications** (If symptoms are associated with certain foods or drinks);
    - * ***Avoid*** **foods/drinks** *may* ***reduce*** **LES pressure**;
      - **Caffeine** (**Coffee** and **Cola**), **Alcohol**, **Chocolate**, **Garlic**, **Onion** & **Peppermint**.
    - * ***Avoid*** **foods/drinks** *may* ***cause*** **irritants** to the **oesophageal mucosa**;
      - **Spicy foods**, **Orange juice**, **Tomato juice** and **Coffee**.
    - * ***Reduce*** **fat intake** (*high-fat meals slow gastric emptying*).
    - * ***Avoid*** **eating 2–3 hours before bedtime**.
    - * ***Remain*** **upright** ***after*** **meals**.
  - **B) Weight loss if overweight**. **C) Reduce or discontinue nicotine use in tobacco products**.
  - **D) Elevate head of bed**. **E) Avoid tight-fitting clothing** (decreases intra-abdominal pressure).
  - **F) Avoid medications** ***that may*** **reduce LES pressure**, **delay gastric emptying**, or cause **direct irritation**: **NSAIDs**, **Nicotine**, **Nitrates**, **Calcium Channel Blockers**, **Anticholinergics**, **Tetracycline**, **Theophylline**, **alpha/beta-blockers**, **Benzodiazepines**, **Opiates**, and **Tricyclic antidepressants**.

Pharmacological Therapy

Antacids

Aluminium Hydroxide [$Al(OH)_2$]	**Magnesium Hydroxide** [$Mg(OH)_2$]
Calcium Carbonate [$CaCO_3$]	**Sodium Bicarbonate** [$NaHCO_3$]

- # **Antacids**; are ***weak bases*** that *react with* **gastric acid** to form **water** and a **salt**.
- # ***reduce*** **pepsin** ***activity***, *because* **pepsin** is ***inactive*** at a **pH > 4**.
- # ***Mechanism of action***; **Neutralizing** **gastric acid** and ***decrease*** of **pepsin**.
- # # **Aluminium**; **Constipation** # # **Magnesium**; **Diarrhea**
- # # **Magaldrate**; is a **hydroxy-magnesium aluminate**; ***No*** **diarrhea** – ***No*** **constipation**
- # # ***Formulations***; **capsules**, **tablets**, **chewable tablets** and **suspensions**.
  - # # **Maalox®**; **Aluminium Hydroxide** + **Magnesium Hydroxide** (**Magaldrate**).
  - # # **Maalox® plus**; **Magaldrate** + **Simethicone** (***anti flatulence***).
  - # # **Epicogel®**; **Magaldrate** + **Dimethicone** (***anti flatulence***).
  - # # **Mucogel®**; **Magaldrate** + **Oxethazaine** (***local anesthetic***).
  - # # **Gaviscon®**; **Potassium Bicarbonate** + **Sodium Alginate** (***physical barrier*** *to* **acid**); ***anti-refluxant*** **Alginic Acid**, ***forms*** a ***viscous layer*** on ***top of*** **gastric contents** to act as a ***barrier***; used ***after meal***.
- # # ***Advantages***; ***Rapid*** **onset of action**.
- # # ***Disadvantages***; ***Short*** **duration of action** (*need frequent dosing*).
- # # ***Drug interactions***; ***Chelation***; *reduce absorption of*; **Fluoroquinolones** & **Tetracyclines**.

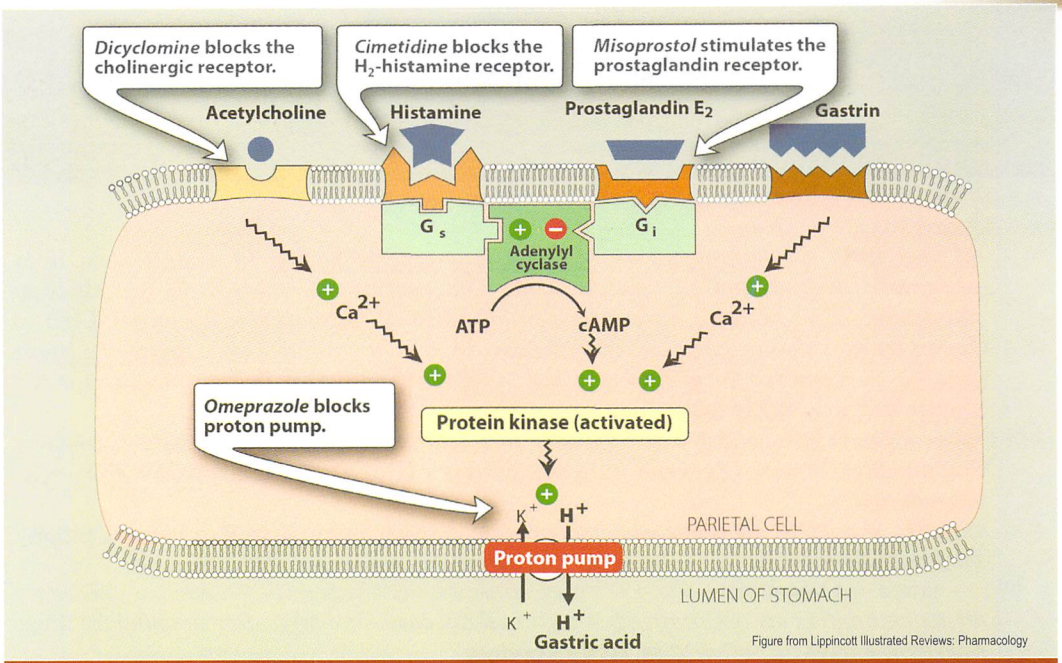
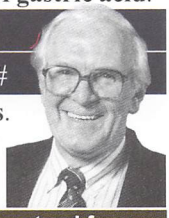


Figure from Lippincott Illustrated Reviews: Pharmacology

H_2-receptor Antagonists (H2RAs)

- The **H_2-receptor Antagonists (H_2RAs)** are ***reversibly inhibit*** **histamine-2 receptors**, ***block*** the ***stimulatory effect*** of **Histamine** on **gastric parietal cell**, ***decreasing*** **production of gastric acid**.

Cimetidine (Tagamet®)	**Ranitidine** (Zantac®)#
Nizatidine (Ulcfree®)#	**Famotidine** (Antodine®)#



- **Cimetidine** is ***largely replaced*** by ***other*** **H_2 receptor blocker** *due to* **side effects**.
- ***Dose reduction*** is **required** in ***moderate*** to ***severe*** **renal dysfunction** and ***severe*** **hepatic impairment**.

Sir James Black was awarded the Nobel Prize for Medicine in 1988 for work leading to the development of Propranolol & Cimetidine

Drug	Relative potency	Usual dose	Parenteral form
Cimetidine	1	400 mg twice or 800 mg at bedtime	50 mg
Ranitidine	4-10	150 mg twice or 300 mg at bedtime	50 mg
Nizatidine	4-10	150 mg twice or 300 mg at bedtime	Not available
Famotidine	20-50	20 mg twice or 40 mg at bedtime	20 mg

Therapeutic Uses;

1) **Peptic Ulcer Disease (PUD)**: **PPIs** have ***largely replaced*** **H_2RAs**
   - **H_2RAs** ***used*** in **Zollinger–Ellison Syndrome (ZES)**; is a ***gastrin-secreting tumor*** of the **pancreas** that ***stimulates*** the **acid-secreting cells** of the **stomach**, cause **mucosal ulceration**.
2) **Gastroesophageal Reflux Disease (GERD): H_2RAs** is ***less efficacious than*** **PPIs**.
3) **Non-ulcer Dyspepsia**: ***Commonly used*** for **dyspepsia** ***not caused*** by **peptic ulcer**.
4) **Acute Stress Ulcers**: **IV infusion** (**PPIs** are ***favor*** for this indication).

H_2-antagonists are ***extremely*** **safe drugs**. ***Pregnancy*** ⇨ **FDA category B**.

Side effects; occur in > 3% of patient; **diarrhea**, **headache** & **fatigue**.

Cimetidine ***inhibits*** binding of **Dihydrotestosterone** to **androgen receptors** (***Anti-androgenic effect***) and ***increase*** **serum prolactin**, ***long term use*** may *cause*;
   - In ***male;*** **Impotence** (*Anti-androgenic effect*) and **Gynecomastia** (*Increase prolactin*).
   - In ***female*** **Galactorrhea** (*Increase prolactin*) and **Amenorrhea**.

- ***Rapid*** **IV infusion** of **H_2-antagonists** may ***rarely*** cause **bradycardia** and **hypotension**.

Proton Pump Inhibitors (PPIs)

Omeprazole (Losec®)# (Pepzol®)# (Omez)#	**Esomeprazole** (Nexium®)#
Lansoprazole (Lanzor®)#	**Dexlansoprazole** (Dexilant®)#
Pantoprazole (Controloc®)# (Pantoloc®)#	**Rabeprazole** (Pariet®)#

All six* proton pump inhibitors (PPIs)** are *effective* ***orally.

All six* PPIs** are ***prodrugs.

All oral* PPIs** are ***formulated as **acid-resistant enteric coated** to ***protect*** them from ***premature*** **degradation** by **gastric acid**; The **coating** is ***removed*** in the **alkaline *duodenum***, & the ***prodrug***, a **weak base**, is ***absorbed*** & ***transported*** to the **parietal cell**.

Omeprazole, **Lansoprazole** and **Esomeprazole** is *also available as* a ***gastro-resistant granules*** as a ***powder for*** **oral suspension** or **tablet formulation** that ***disintegrates*** in the **mouth**, or it may *mixed with* **water**.

Omeprazole is also available as a ***powder formulation*** (**capsule** or **packet**) that contains **Sodium Bicarbonate** (**Zegerid®**) to ***raise*** **gastric pH** to ***protect*** **Omeprazole** *from* **acid *degradation***.

All* PPIs *should be administered *approximately* **30-60 minutes *before*** a **meal** (usually breakfast); ***bioavailability*** of all agents is decreased *approximately* **50%** by ***food***.

[PPI → no food → ↑ bioavailability → food → ↑ pump activity and ↑ acid secretion → PPI action → ↑ efficacy]

Full acid inhibiting are *occur* ***after* 3–4 days** of ***daily dose***, similarly, ***after stopping*** the drug, it takes **3–4 days** for ***full acid secretion*** to *return*.

Mechanism; - **Active drugs** of **proton pump inhibitors *blocks* proton pump** by ***forms*** a ***stable* covalent bond** (***irreversible***) with the **H^+/K^+-ATPase enzyme**.

- ***At least* 18 hours** are *required for* ***resynthesized*** of ***new* H^+/K^+-ATPase enzyme**, and **acid *secretion*** is ***inhibited*** *during this* **time**.

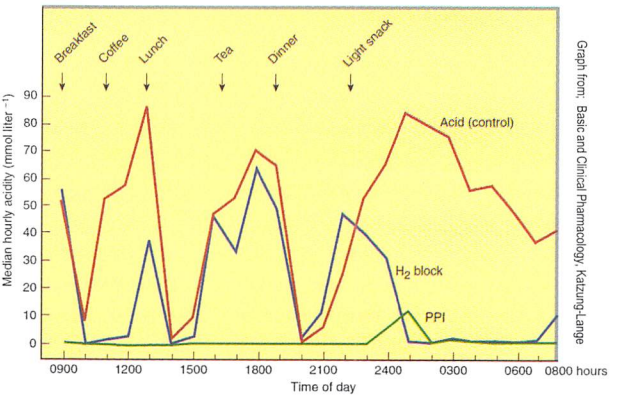
Drug	Relative potency	Usual dose	Parenteral form
Omeprazole	1	20-40 mg once/d	
Esomeprazole	1.6	20-40 mg once/d	IV 20, 40-mg/vial
Lansoprazole	0.9	15-30 mg once/d	IV 30 mg/vial
Dexlansoprazole	data not available	30-60 mg once/d	
Pantoprazole	0.23	20-40 mg once/d	IV 40 mg/vial
Rabeprazole	1.82	10-20 mg once/d	

Therapeutic Uses;

1) **Gastroesophageal Reflux Disease (GERD)**; **Gold-Standard**
2) **Peptic Ulcer Disease (PUD)**; ***More rapid*** **symptom relief** and ***faster* ulcer healing** *than* **H_2RAs**.
3) **Non-ulcer Dyspepsia**.
4) **Acute Stress Ulcers**.

Red; Twenty-four-hour median intragastric acidity pre-treatment.
Blue; After 1 month of treatment with ranitidine, 150 mg twice daily.
Green; After 1 month of treatment with omeprazole 20 mg once daily (PPI).

- ***Notes***;
  - **H_2-receptor antagonists** have a ***marked effect*** on **nocturnal acid secretion** but only a ***modest* effect** on **meal-stimulated secretion**.
  - **Proton pump inhibitors (PPIs)** ***markedly suppress*** **meal-stimulated** and **nocturnal acid secretion**.



Side effects; **PPIs** are ***extremely safe***, **diarrhea**, **headache**, and **abdominal pain** are reported only in **1–5%** of **patients**.

Pregnancy ⇨ ***Enough*** **data** to *suggest* that **PPIs** therapy is ***safe*** *during* **pregnancy**, *but* **Antacids** and **H_2-receptor antagonist** are *superior* to **use**.

- **Respiratory** and **Enteric Infections**; **Gastric acid** is an ***important barrier*** to **colonization** and ***infection*** of the **stomach** and **intestine** from *ingested bacteria*.

Long-term side effects; # # # # # # # # **PATIENT COUNSELLING** # # # # # # #

{**Hypochlorhydria** or **achlorhydria**; **low** or **absent HCl production**}

- **Gastric acid** is ***important for*** **absorption** of; **Vitamin B_{12}**, **Iron**, **Calcium** and **Magnesium**;
- ***Long term use of*** **PPIs**; ***risk for*** **osteoporosis** (**Calcium Citrate** is the ***preferred*** **calcium supplement** in ***patients taking*** **PPIs** and ***ensure adequate*** **Vitamin D**), ***severe*** **life-threatening hypomagnesemia** with *secondary* **hypocalcemia**.
- *Effects of* **Vitamin B_{12}** and **Iron** ***malabsorption*** is ***clinically*** **insignificant**.

Long term use of **PPIs** (*especially* **Omeprazole**) have also been *associated with* ***several cases*** of **acute interstitial nephritis**.

- ***All*** **PPIs** are ***metabolized by*** **CYP2C19** and **CYP3A4**, ***because*** of the ***short half-lives*** of (*about 1.5 hours*) **PPIs**, ***clinically*** **significant drug interactions** are ***rare***.

Drug Interactions; !!!

1) **Drugs** *with* **pH-dependent** ***absorption***; **Itraconazole** & **Protease inhibitors**.
2) **Inhibition of CYP450**; **Warfarin**, **Diazepam**, **Phenytoin** and **Theophylline**.
3) **Inhibition of CYP2C19** # # # # # # # # # # # # # #
   - **Clopidogrel** (***antiplatelet***) is a **prodrug** that ***requires*** **CYP2C19**.
   - ***In 2009***, the **FDA** issued a public-health ***warning*** about the ***possible interaction*** between **Clopidogrel** and **Omeprazole**.
   - ***Recent*** (***2015***) **meta-analysis study**; In summary, suggest that the highly controversial ***interaction between*** **PPIs** (**Omeprazole**) and **Clopidogrel** observed in platelet aggregation studies has ***no clinical significance***.
4) ***high-dose*** **IV Methotrexate**; ***Higher risk*** of **methotrexate toxicity**; switch to **Ranitidine** if needed, for **2 days** ***before*** and ***after*** **Methotrexate** administration.

- **H_2 blockers** *can be used* ***with*** **PPIs** in ***some*** **severe cases**; ***which of one taken first***?
- **Proton pump inhibitors (PPIs)** *may* ***mask*** **early symptoms of gastric cancer**!

Prostaglandins

Misoprostol (Cytotec®)# (Misotac®)#

Misoprostol is a **PGE_1 analogue**, ***with*** **oxytocic** ***properties***.

It is **approved** for ***use*** in the ***prevention*** **of NSAID-induced gastric ulcers**;

It ***produces*** **uterine contractions** and is ***contraindicated*** *during* **pregnancy**.

Off-label: **labor induction**, **abortion**, **missed miscarriage** & **postpartum bleeding**;

- ***Routes of administration***; include oral, vaginal, sublingual, buccal, or rectal.
- In **abortions** ***mainly*** **used in combination** with **Mifepristone** (***Antiprogestin***).

Dear pharmacists; This drug is prescribed only by obstetricians and gynaecologists by a trusted prescription; So don't prescribe this drug by any way because may be used by prostitutes for abortion (illegally).

Mucosal Protective Agents

Sucralfate (Gastrofait®)#

Sucralfate is a ***sucrose sulfate-aluminium complex*** that ***binds*** to the **ulcer**, ***creating*** a **physical barrier** that ***protects*** **ulcer** *from* **gastric acid**, *allowing* the **ulcer** *to* **heal**.

Require **acidic pH** for ***activation***. # # ***Dose***; **1- 2 gm twice daily**.

Bismuth Subsalicylate (Pepto-Bismol®)

Antimicrobial actions, ***inhibits*** **pepsin activity**, ***increases*** **mucus secretion**, ***coat*** and ***protect*** the **ulcer**. **Bismuth compounds** *may cause* a **black discoloration** of **tongue** & **stool**.

Treatment of *H. pylori* Associated Ulcers

First Line		
Standard Triple Therapy	**Duration**	**Efficacy**
* PPI + Amoxicillin 1 g BID + Clarithromycin 500 mg BID OR * PPI + Metronidazole 500 mg BID + Clarithromycin 500 mg BID	10–14 Days	70–85%
Sequential Therapy		
* PPI + Amoxicillin 1 g BID for **5 days**, then PPI, Clarithromycin 500 mg BID + Tinidazole 500 mg BID for **5 days**	10 Days (5+5)	> 90%
Second Line		
Non–bismuth-based Quadruple Therapy		
* PPI + Amoxicillin 1 g BID + Clarithromycin 500 mg BID + Tinidazole 500 mg BID (*or* Metronidazole 500 mg BID)	10 Days	90%
Bismuth-based Quadruple Therapy		
* Bismuth Subsalicylate 525 mg QID + Metronidazole 500 mg TID + Tetracycline 500 mg QID + PPI BID	14 Days	75–90%
* {Bismuth Subcitrate 420 mg + Tetracycline 375 mg + Metronidazole 375 mg (Pylera®) QID} + PPI BID	10 Days	85–92%
Levofloxacin-based Triple Therapy		
* PPI + Amoxicillin 1 g BID + Levofloxacin 500 mg once daily	10 Days	-

PPI = Omeprazole 20 mg BID or Lansoprazole 30 mg BID or Esomeprazole 40 mg once daily or Rabeprazole 20 mg PO BID (Pantoprazole or Dexlansoprazole *not* FDA-approved indication for *H. pylori* eradication).

BID = twice daily; PO = orally; PPI = proton pump inhibitor; QID = 4 times/day; TID = 3 times/day

- Metronidazole can be *substituted for* Amoxicillin or Clarithromycin in patients with **penicillin** or **macrolide *allergy*** for the **triple-drug regimens**, treat for **14 days** in this instance.

Primary Prevention of NSAID-Induced Ulcers

→ If ***low* CV risk** and:
- ***Low* GI risk** → **NSAID** (*lowest dose*).
- ***Moderate* GI risk** → **NSAID + PPI** OR **Misoprostol** (800 mcg/day in divided doses).
- ***High* GI risk** → **COX-2 inhibitor + PPI** OR **Misoprostol** (800 mcg/day in divided doses).

→ If ***high* CV risk** (***requirement for** low-dose* **Aspirin**) and:
- ***Low* GI risk** → **Naproxen + PPI** OR **Misoprostol**.
- ***Moderate* GI risk** → **Naproxen + PPI** OR **Misoprostol**.
- ***High* GI risk** → **Avoid NSAIDs** OR **COX-2 inhibitors**.

Secondary Prevention of NSAID-Induced Ulcers

1) **PPIs**; ***Drugs of choice***, **Combination product** may be used such as Vimovo® contains Esomeprazole with Naproxen in the ***same tablet*** (375 mg/20 mg or 500 mg/20 mg).
2) Misoprostol: *effective as* **PPIs** but require ***several* doses** *per* **day** and **high doses** *cause* **diarrhea** and **abdominal pain**.
3) ***Combination*** of a **COX-2 inhibitor + PPI**.
4) **H_2RAs**; ***less than*** Misoprostol and **PPIs** in ***healing*** and ***preventing*** **recurrence**.

Promotility (Prokinetic) Agents

- ***Promotility*** (***Prokinetic***) ***agents*** are a type of drug which ***enhance*** **gastric emptying** and ***enhance*** **intestinal contractions**.
- They are **used** to *relieve* **GI symptoms** such as **abdominal discomfort**, **bloating**, **constipation**, **heart burn**, **nausea** and **vomiting**.
- **Prokinetic Uses**; **Delayed stomach emptying** in ***diabetes*** or ***following surgery*** and **GERD**, **vomiting**, **indigestion**, **dyspepsia** and **hiccup**.

Metoclopramide (Primperan®)#

Metoclopramide is a ***peripherally*** and ***centrally*** ***dopamine antagonist***.
Metoclopramide ***increases*** **LES pressure** and ***accelerates*** **gastric emptying** (***does not improve*** **oesophageal clearance**).
Formulations; Tab, supp, syrup and injection (*not* SC).
Antiemetic properties; ***block*** **stimulation** of the medullary **chemoreceptor trigger zone** (**CTZ**) by **Dopamine** or **Dopamine-like agents** (**L-dopa** or **Apomorphine**).
Uses; - **Nausea** and **vomiting**.
- **Delayed stomach emptying** in ***diabetes*** (**diabetic gastric stasis**) or ***following surgery*** and in **GERD**.
- ***Also used*** to ***treat*** **migraine headaches**.

Dose *in* **GERD**; **10-15 mg orally** ***up to*** **4 times** a **day 30 min**. ***before*** **meals** and at **bedtime**.
Side effects; **Dizziness**, **fatigue**, **somnolence**, **drowsiness**, **extrapyramidal symptoms** (**EPS**) and **hyperprolactinemia**.
Children; **0.1-0.2 mg/kg/dose**; **3** to **4** ***times*** **daily**.
FDA warning; **Metoclopramide** can ***cause*** **tardive dyskinesia** (***Treatment with*** **Metoclopramide** for ***longer than*** **12 weeks** ***should be*** **avoided**).

Domperidone (Motilium®)#

Domperidone is a ***peripherally*** ***dopamine antagonist***.
Formulations; Tab, supp, syrup, sachets and injection (*not* SC).
Domperidone ***may*** ***relieve*** **nausea** and **vomiting** by ***improve*** **upper GIT** ***motility***.
Domperidone *promote* **lactation** by ***blocks*** **dopamine receptors** in the *anterior* **pituitary gland** *increasing* **release** of **Prolactin** which in turn *increases* **lactation** (not covered by BBB).
Dose; **10 mg orally 3** ***times*** **daily 30 minutes** ***before*** **meals** and at **bedtime**.
Children; **0.25-0.5 mg/kg/dose**; **3** to **4** ***times*** **daily**.
DON'T ***use*** **30 mg Domperidone supp** in **children < 10 years**; ***Fatal*** **QT prolongation**.
Side effects; ***Fatal*** **QT prolongation** (mostly when used with CYP3A4 inhibitors such as; **Itraconazole** and **Ketoconazole**, **Erythromycin** and *certain other* **macrolide**).

Cisapride (Motiprid®)

- **Cisapride** is a ***gastroprokinetic agent***, it acts ***as*** a ***Serotonin*** **5-HT4 receptor** ***agonist***.
- ***Stimulation*** of the **serotonin** ***increases*** **Acetylcholine** ***release*** in the **enteric nervous system**.
- **Cisapride** ***improve*** **oesophageal clearance**.
- **Cisapride** is ***no longer available***; ***life-threatening*** **cardiac arrhythmias**, when used in ***combination*** with drugs ***inhibiting*** **CYP3A4**.

Bethanechol (Urotone®)

- **Bethanechol** is a ***parasympathomimetic choline carbamate*** that ***selectively stimulates*** **muscarinic receptors** *without any* effect on **nicotinic receptors**.
- **Bethanechol** has ***limited value*** in the ***treatment of*** **GERD** because of *unwanted* ***side effects***, is ***not*** *routinely* ***recommended*** for **GERD**.
- It is ***used*** in **postoperative non-obstructive GIT** and **urinary tension**.
- ***Side effects***; **Diarrhea**, **blurred vision**, **abdominal cramping**.

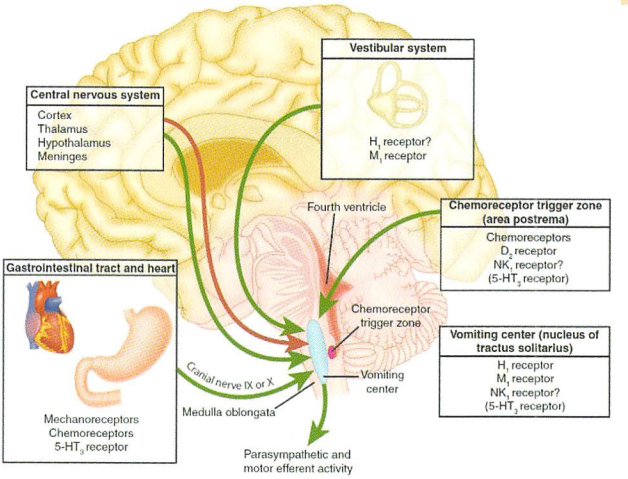
Antiemetic Agents

- *Nausea*: *Unpleasant sensation* of the ***imminent need*** *to* **vomit**; ***may*** or ***may not*** *lead to* the *act of* **vomiting**.
- *Vomiting* (*emesis*): *Involuntary forceful expulsion* of **gastric contents** *through the* **mouth**.
- **Nausea** and **vomiting** *may occur* ***separately*** or ***together***.
- *Nearly* **70-80%** of ***patients*** who undergo **chemotherapy** *experience* **nausea** and/or **vomiting**.
- About **50-80%** of **pregnant women** *experience* **nausea** and/or **vomiting** *during* the **first trimester** of **pregnancy** (due to *high levels* **human chorionic gonadotropin**; **hCG**).
- **Stimuli** *for* **nausea** are **processed** *through* ***several*** **major anatomic areas**, each of which has various receptors associated with input to the medullary vomiting center.
- There are **4 important sources** of afferent ***input*** to the **vomiting center**:
  1) **Chemoreceptor Trigger Zone** (**CTZ**); **D_2, 5-HT_3** and **NK_1 receptors**.
  2) **Vestibular System**; **H_1** and **M_1 receptors**.
  3) **Cerebral Cortex**; **Anxiety, stress** and **psychiatric disorders**.
  4) **Visceral Stimuli** (**GIT**); **5-HT_3 receptors**.

D_2 - 5-HT_3 - H_1

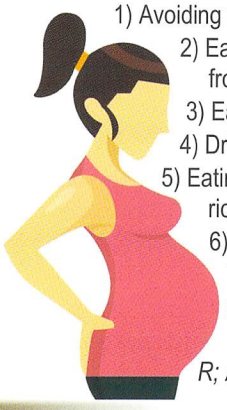
Vomiting Center

M_1 - NK_1



Lifestyle Management of NVP

- **Lifestyle Management** of **Nausea** *and* **Vomiting during Pregnancy** (**NVP**);



1) Avoiding foods and smells that trigger nausea.
2) Eating a couple of soda crackers before wake up. Allow some time for digestion, and wake up from bed slowly once are ready.
3) Eating smaller meals more frequently throughout the day instead of three big meals.
4) Drinking less water/fluids with meals, and instead drink them between meals.
5) Eating more dry, plain foods such as white rice, dry toast, or a plain baked potato instead of richer, creamier foods.
6) Sucking on hard candy.
7) Keeping rooms well ventilated or take time to go outside to get some fresh air.
8) Sniffing ginger or lemons, or drinking ginger ale or lemonade, which can help ease the feeling of nausea.

R; American Pregnancy Association

Antiemetic Agents

Dopamine (D_2) Antagonists

Prochlorperazine (Emedrotec®)

- **Prochlorperazine** and **Promethazine** are **Phenothiazines** are ***antipsychotic agents***.
- **IV Phenothiazines** provided ***quicker*** and ***more complete*** **relief** in **emergency department**.
- ***Dose*** of ***antiemetic effect*** is *approximately* a ***third*** of that than its **dose** *for* **psychosis**.
- ***Formulations***; Tablets, syrup, suppositories and injection (*not* SC).
- ***Side effects***; **Extrapyramidal symptoms (EPS)** and **hypersensitivity reactions**.

Promethazine (Phenergan®)

- ***Antiemetic mechanism***; **antidopaminergic**, **anticholinergic** and **antihistaminergic** ***activity***.
- ***Formulations***; Tablets, suppositories and injection.
- ***Side effects***; **EPS**, **hypersensitivity reactions**, **sedation**, and **anticholinergic effects**.

Haloperidol (Haldol®)# | Droperidol (Inapsine®)

- ***Formulations***; **Haloperidol**; Injection, tablets. **Droperidol**; Injection.
- ***Side effects***; **Extrapyramidal symptoms (EPS)**, ***fatal*** **QT prolongation** (ECG monitoring for 2 to 3 hours after administration).

Metoclopramide (Primperan®)#

Metoclopramide is a **Substituted Benzamides**; ***peripherally*** and ***centrally*** ***dopamine antagonist***.
Antiemetic mechanism; ***block*** **D_2 receptors** in **CTZ**.
Pregnancy; **US FDA category B**; ***not recommended due to*** **extrapyramidal symptoms (EPS)**.
Side effects; **extrapyramidal symptoms (EPS)**; *long-term use* (can ***cause*** **tardive dyskinesia**).

Domperidone (Motilium®)#

Domperidone is a ***peripherally*** ***dopamine antagonist***.
Domperidone ***may*** ***relieve*** **nausea** and **vomiting** by ***improve*** **upper GIT** ***motility***.
Domperidone *promote* **lactation** by ***blocks*** **dopamine receptors** in the *anterior* **pituitary gland** *increasing* ***release*** of **Prolactin** which in turn *increases* **lactation**.
Pregnancy; **US FDA category C**; ***not recommended due to*** **QT prolongation**.
Side effects; ***Fatal*** **QT prolongation** (mostly when used with CYP3A4 inhibitors such as; **Itraconazole** and **Ketoconazole**, **Erythromycin** and *certain other* **macrolide**).
Contraindications; **CYP3A4 inhibitors**, **Prolactin secreting pituitary tumor**, **Mechanical bowel disorders** (such as bowel obstruction, gastrointestinal hemorrhage or bowel perforation).

Olanzapine (Zyprexa®)#

- **Olanzapine** is an ***atypical antipsychotic***, it is ***block*** **5-HT_{2A}** and **D_2 receptors**.
- **Olanzapine** can be ***used*** in ***combination*** with to **standard antiemetics** such as **Palonosetron** and **Dexamethasone**, for ***prevent*** **acute chemotherapy-induced nausea & vomiting (CINV)**.

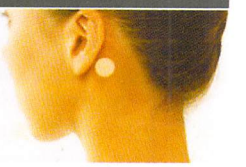
Serotonin 5-HT_3 Receptor Antagonists (5-HT_3-RAs)

Ondansetron (Zofran®)# (Danset®)# | Granisetron (Kytril®)# (EM-EX®)#

Uses; **nausea/vomiting**; **cancer chemotherapy**, **radiation therapy**, **surgery** or **postoperative**.
Off-label used to treat **morning sickness** & **hyperemesis** in **pregnancy** (**category B**).
Ondansetron *may* ***increase*** **risk** of **cleft lip and palate** ***defects*** *when* **used** ***during*** **Pregnancy**!
Formulations; - **Ondansetron**; Tablet, disintegrating tablet, solution and injection.
Ondansetron ***injection*** is ***same*** **concentration** but ***different*** **volume**.
- **Granisetron**; Tab., solution, patch & injection. - **Dolasetron**; Tab. & injection.

Antimuscarinic

Scopolamine or Hyoscine (Transderm Scop®)



- Scopolamine, is a *tertiary amine* **plant alkaloid** (natural belladonna alkaloids) *produces* **peripheral effects** ***similar to*** those of Atropine.
- Scopolamine is **one** of the ***most*** **effective anti–motion sickness drugs**.
- ***The therapeutic*** **use** of **scopolamine** is *limited to* **prevention** ***of*** **motion sickness** and **postoperative nausea and vomiting**.
- It is available as a topical patch (Transderm Scop®) that provides effects for up to 3 days.

Antihistamines

Diphenhydramine (Dramenex®)#	**Dimenhydrinate** (Dramamine®)#
Meclizine (Navidoxine®)#	**Cyclizine** (Emetrex®)#
Doxylamine (Vomibreak®)#	**Promethazine** (Phenergan®)#

This agents are ***most effective*** **antihistamines agents** for ***prevention*** of the ***symptoms*** of **motion sickness** and **vertigo** (***prevent*** **nausea** and **vomiting**), ***used*** **30–60 minutes** *before* **travel**.

Antiemetic mechanism; ***due to*** block H_1 & M_1 in ***vestibular system*** & may affect at **CTZ**.

Brands; **FIRST CHOICE**; **nausea and vomiting of pregnancy** (NVP)

Navidoxine®; Meclizine + Vitamin B6 (Pyridoxine); pregnancy category B.

Emetrex®; Cyclizine + Vitamin B6; pregnancy category B.

Diclegis® or Vomibreak®; Doxylamine + Vitamin B6; pregnancy category A.

Systemic acute **toxicity**, ***especially*** in **young children**, *including* **hallucinations**, **excitement**, **ataxia**, and **convulsions**. ***So***, (Emetrex® Ampoule) is **NOT** recommended in **CHILDREN** younger than **6 years** to prevent vomiting (**Ondansetron** is ***safer***).

Corticosteroids

Methylprednisolone (Depo-Medrol®)#	**Dexamethasone** (Epidron®)#

- ***Acute*** and ***delayed*** **nausea** and **vomiting** in ***moderately*** to ***highly*** **emetogenic chemotherapy**.

Brands; **Cortigen-B_6®**; **Corticoadrenal Extract** + (**Pyridoxine**) **Vitamin B_6** *was available* to ***control*** **nausea** and **vomiting** in and ***may use*** *during* **pregnancy** or **children** or **paediatrics**.

Cannabinoids

Dronabinol (Marinol®)	**Nabilone** (Cesamet®)

- They are a synthetic **Δ9-Tetrahydrocannabinol** (**THC**) ***analog***, ***used*** in ***severe*** **nausea** and **vomiting** *caused by* **cancer chemotherapy** (**CINV**).
- Can be ***used to*** **stimulate appetite** in ***patients with*** **AIDS**.

Neurokinin-1 (NK_1) Receptor Blockers

Aprepitant (Emend®)	**Netupitant** (Akynzeo®)	**Rolapitant** (Varubi®)

- **Aprepitant** is *usually* ***combined*** with **Dexamethasone** and a **5-HT_3-RAs** in ***preventing*** **CINV**.
- **Netupitant** was ***approved in*** **combination** with **Palonosetron**; Akynzeo® in ***preventing*** **CINV**.
- **Rolapitant** is approved in ***combination*** with ***other*** **antiemetic agents** in ***adults*** for the ***prevention*** of ***delayed*** **nausea** and **vomiting associated** with ***initial*** and ***repeat courses*** of **emetogenic cancer chemotherapy**, ***including***, ***but not limited to***, **highly emetogenic chemotherapy**.

Herbal

Ginger

Ginger may ***use*** to ***relieve*** **nausea** and **morning sickness** *during* **early pregnancy** (**NVP**), **women** ***should not*** *consume* **large amounts** of **ginger**, as it can cause **uterine contractions**.

Antidiarrheal Agents

- **Diarrhea** [dia-rrho-ea] or **Diarrhoea**; is ***characterized by*** **loose, watery stools** or a ***frequent*** **need** to ***have*** a **bowel movement**.
- **Diarrhea** *remains* the ***second*** *leading* **cause** of **mortality** ***after*** **pneumonia** in ***infant***.
- ***Most common*** **cause** is an **infection** of the ***intestines*** (**virus, bacteria** or **parasite**).
- ***Viral diarrhea*** is ***most common*** in **young children** (*rotavirus* and *astrovirus*).
- ***Management of diarrhea*** *focuses on* ***preventing*** *excessive* **water** and **electrolyte** ***losses***, **dietary** *care*, *relieving* **symptoms**, ***treating*** **curable causes**, and ***treating*** **secondary disorders**.

Definition; ***Alteration in*** a ***normal*** **bowel movement** ***characterized by*** an ***increase in*** the **water content, volume,** or **frequency** (***more than*** **3** *per* **day**) of **stool**.

- ***Acute Diarrhea***; ***Less than*** **14 days**. - ***Chronic*** (**or** ***Persistent***) ***Diarrhea***; ***More than*** **14 days**.

- **Traveler's Diarrhea** (**TD**); is an **acute diarrhea** *caused by* **eating** ***contaminated*** **food** or **drinking**, *when* **traveling**.

Pharmacological Therapy

Rehydration

- **Sodium** and **Glucose** are ***key ingredients*** of **oral rehydration solutions** because they have *active uptake* into the **intestinal mucosa** *even* ***during active*** **diarrhea**. This ***results in*** **water** being ***pulled back into*** **circulation**.
- ***Dose*** **and** ***Administration*** (**Rehydran-N**®) (**Hydro-safe**®);
  - ***Dissolve*** the **content** of this **sachet** in **200 ml** of **water** (glass of water) to *form* **Oral Rehydration Solution** (**ORS**).
    - For ***prevention***; Give 50 ml solution per stool motion.
    - For ***treatment***; Give the solution to the child to drink as he or she can, and continue breast feeding or normal feed.

Antimicrobial Agents

Antibiotics

- **Cefixime** (**Suprax**®); ***potent*** **oral** ***3rd generation cephalosporin*** with ***high*** **gram -ve coverage**.
- **Ceftriaxone** (**Rocephin**®) & **Cefotaxime** (**Claforan**®); are ***potent*** **injectable** ***3rd generation cephalosporin*** with *increased* **gram -ve coverage** and ***some*** **gram-*positive*** **bacteria**.
- **Fluoroquinolone antibiotics**; *such as* **Ciprofloxacin** (**Cipro**®) and **Levofloxacin** (**Tavanic**®); ***Drug of choice*** for **traveler's diarrhea**.
- **Azithromycin** (**Zithromax**®); ***good choice*** in **traveler's diarrhea** for ***pregnant women*** and **children**.
- **Rifaximin** (**Xifaxan**®); also used in **traveler's diarrhea**.
- **Sulfamethoxazole/Trimethoprim** (**Septrin**®); Can be used in **traveler's diarrhea** ***prophylaxis***.
- **Vancomycin** (**Vancomycin**®); ***orally*** for **antibiotic-associated colitis** (**pseudomembranous colitis**).
- **Doxycycline** (**Vibramycin**®); is a ***good choice*** for ***Vibrio cholerae*** **infection** and can be used in **traveler's diarrhea** ***prophylaxis***.
- **Neomycin** (*not absorbed from GIT*) and **Streptomycin**; can be used ***orally*** in **traveler's diarrhea**.
- **Bismuth Subsalicylate** (**Pepto-Bismol**®); Used in **traveler's diarrhea** ***prophylaxis***.
- **Nifuroxazide** (**Antinal**®); is an **oral** ***nitrofuran antibiotic***, is a ***broad spectrum*** **intestinal antiseptic** for the *treatment* of **diarrhea** & **gastroenteritis** (*poorly absorbed from the GIT, act mainly locally*).

Antiprotozoal

- **Nitazoxanide** (**Alinia**®); **diarrhea** due to **Cryptosporidiosis** or **Giardiasis**.
- **Metronidazole** (**Flagyl**®); is an ***antibiotic*** and ***antiprotozoal agent***, it is effective against wide range of microorganisms, is a ***good choice*** for **diarrhea** due to; **Amoebic dysentery** or **Amebiasis**, **antibiotic-associated colitis** and **Giardiasis**. **Tinidazole** (**Fasigyn**®), **Secnidazole** (**Flagentyl**®) and **Ornidazole** (**Tibezole**®); are an ***antibiotic*** and ***antiprotozoal agent*** like **Metronidazole**.

Antiparasitic

- **Albendazole** (**Alzental**®), **Mebendazole** (**Antiver**®) and **Flubendazole** (**Fluvermal**®); is a ***broad spectrum*** **anthelmintic agents** used in **diarrhea** *caused by* **worms**.

Antimotility Agents

Loperamide (Imodium®)#

Loperamide is an OTC opioid drug, act as μ receptor *agonist* on *large intestine* (*not* pass BBB)
Pregnancy; **Category B**.
Side effects; *increase* **risk** of **toxic megacolon** (*acute colonic distension*) and **paralytic ileus**.
Contraindications; ***high*** **fever**, ***bloody*** or ***black*** **stool** and in **children less than 2 years**.

Diphenoxylate/Atropine (Lomotil®)#

Diphenoxylate is a *prescription* **opioid drug**, act as **μ receptor** *agonist* (*cross* BBB and may cause **physical dependence** with high doses). *Pregnancy*; **Category C**.
Side effects; ***Atropine like effects*** (dry mouth, headache and blurred vision).
Contraindications; ***high*** **fever**, ***bloody*** or ***black*** **stool** and in **obstructive jaundice**.

Antisecretory Agents

Bismuth Subsalicylate (Pepto-Bismol®)

- **Antisecretory**, **anti-inflammatory**, and **antibacterial** *effects*.

Racecadotril (Hidrasec®)#

- **Racecadotril** is an *antisecretory agent* act as ***peripherally*** **enkephalinase inhibitor**, lead to *increase* **Enkephalins** (**endogenous opioids**) ***levels***, *lead to* ***inhibits*** **fluid/electrolyte depletion** (NOT act on **motility**).
- **Racecadotril** is a *prodrug* which is ***converted to*** **Thiorphan** is the ***active*** **metabolite**.
Racecadotril is **used** as *adjuvant therapy* to **oral rehydration solution** (**ORS**) in **acute diarrhea** in **children** (*over 3 months*) and **adult**; ***reduce frequency*** and ***duration*** of **diarrhea**.
Dose; **1.5 mg/kg 3 times** ***daily*** (10 mg sachet; infant – 30 mg sachet; child – 100 mg capsules; adult).

Adsorbent Agents

- **These agents** *act by* *adsorbing* (***binding***) **intestinal toxins** or **microorganisms** and/or by ***coating*** or ***protecting*** the **intestinal mucosa**.

Methylcellulose (Citrucel®)

- **Methylcellulose** is ***not absorbed***, is a ***hydrophilic colloid*** which ***absorbs*** **water** in the **intestines**.

Kaolin-Pectin (Kapect®)# | Diosmectite (Smecta®)

- **Kaolin/Pectin** ***mixture*** is an off-white ***suspension*** ***used for*** **diarrhea**.
- **Kaolin**, is a ***natural*** **hydrated aluminium silicate**, ***not absorbed***, act by ***binds*** to **bacteria** and **toxic substances** in the **GIT**.
- **Pectin** is a ***polyuronic polymer*** extracted from **citrus fruits**, the **mechanism of action** is *unknown*, but it may ***decrease*** **stool softness** (**stool modifiers**) and ***increase*** **viscosity**.
- **Diosmectite** (**Smecta®**) is a ***natural*** **silicate** of **aluminium** & **magnesium** used as **adsorbent**.

Alternative Therapies

Lactase Enzyme

- **Lactase** is an ***enzyme*** that ***aids*** in the ***digestion*** of **Lactose**.
Lactose is in ***dairy foods***, this ***enzyme supplement*** is used to ***break down*** **Lactose** and ***prevent*** **bloating**, **diarrhea**, and **gas** of **lactose intolerance**.
Lactase ***enzyme used*** in **lactose intolerance patient** ***taken with*** **milk** or **dairy product**.

Probiotics (Bacterial Replacement Therapy) (Lacteol® forte)# (ChocBalls®)

- **Probiotics** *restore normal* **intestinal function** & *suppresses* ***growth*** of **pathogenic microorganism**.
Probiotics have been shown to ***decrease*** the **duration** of **infectious** and **antibiotic-induced diarrhea** (*C. difficile*) in ***adults*** and ***children*** (*Not used in severely immunocompromised patients*).

Zinc (Zinc sulfate)

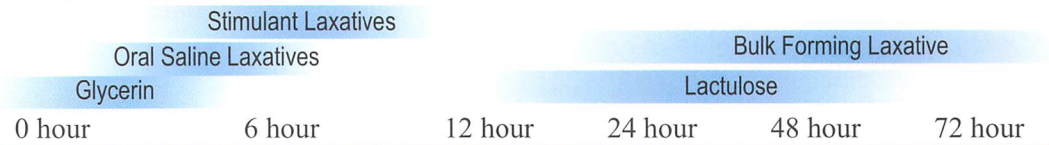
Zinc ***reduce*** the **duration** and **severity** of **diarrhea**, and to ***prevent*** **subsequent episodes**.
WHO recommendations; Children with diarrhea should provide with 20 mg per day of **Zinc supplementation** for 10-14 days (10 mg per day for infants under the age of six months).

Laxatives

- The **definition** of **constipation** *includes* the ***following***;
  - * **Infrequent bowel movements** (*typically* ***less than*** 3 **times** ***per*** **week**).
  - * **Straining** ***during*** **bowel movements** (***difficulty*** *during* **defecation**).
  - * ***Sensation*** of **hard dry stools**.
  - * ***Sensation*** of ***incomplete*** **defecation**.
- **Constipation** can be ***caused*** or ***exacerbated*** *by*;
  - A) **Diet**; Low-fiber diet, low liquid intake, dieting or overuse of coffee and tea may cause constipation.
  - B) **Metabolic** or **Hormonal**; Pregnancy, Diabetes, hyperparathyroidism & hypothyroidism.
  - C) **Structural** (morphological or anatomical); Colon cancer, anal fissures, proctitis (inflammation of the anus and the lining of the rectum), and pelvic floor dysfunction.
  - D) **Neurological**; Autonomic neuropathy, Multiple sclerosis, Parkinson's disease, Spinal cord injury & Stroke.
  - E) **Psychological**; Stress, Depression and Anxiety.
  - F) **Medications**;
    - **Opioids**
    - **Diuretics**
    - **Bile acid sequestrants**
    - **Calcium channel blockers**
    - **Calcium** *supplements*
    - **Antihistamines**
    - **Scopolamine**
    - **Benzodiazepines**
    - **Antacids** (**Al**, **Ca**)
    - **Phenothiazines**
    - **Tricyclic antidepressants**
    - **Benztropine**
    - **Iron** *supplements*
    - **Aluminium**-*containing drugs*
- **Laxatives**, **Purgatives** & **Cathartics**; are terms describing **drugs** that ***promote*** **evacuation** of the **intestine**.

	Laxatives +	Purgatives ++	Cathartics +++
Potency	Powerful	More powerful	Most powerful
Action	Eases defecation	Accelerates defecation	Urgency defecation
End-Stool	Soft stool	Liquefied stool	More liquid stool
Example	**Psyllium**	**Bisacodyl**	**Magnesium Sulfate**

- ***Onset of Laxatives***;



Stimulant (or Irritant) Laxatives

- **Stimulant laxatives** are ***substances*** that act on the **intestinal mucosa** or **enteric nervous system**, ***altering*** **water** and **electrolyte** ***secretion*** and ***stimulate*** **peristaltic action**.
- ***Long-term use*** of **stimulant laxatives** *could lead to* **dependence** and ***destruction*** of the **myenteric plexus** (nerve supply GIT), resulting in **colonic atony** and **dilation**.
- ***Laxative Abuse***; some of the ***less significant*** **adverse effects** of **laxative abuse** include; **dehydration**, **hypotension**, **tachycardia**, **postural dizziness** and **syncope**.
- **Laxative abuse** *can lead* to ***potentially fatal*** **acid-base** and **electrolyte imbalances**.

Senna (Senokot®) (Senna lax®)# (Mentholax®) (Agiolax®)

- Senna is *widely used* stimulant laxative.
- *Active ingredient*; Sennoside is an *anthraquinone glycoside*.

Uses; - *Short-term* relief of *acute or intermittent* constipation.
- *Evacuation* of the bowel *before* surgery or colonic examinations.
- *Prevention* of opioid-induced constipation.

- *Formulations*; oral formula and suppository.
- *Administration*; orally; *once daily* at bedtime.

Onset; 6-12 hours *when given* orally and *within* 2 hours *when given* rectally.

Side effects; *May cause* abdominal cramping, # # Electrolyte Disturbances # #, melanosis coli (pigmentation of the wall of the colon).

Pregnancy; category C; *not recommended*

- *Lactation*; *Not excreted in milk* (safe).
- *Contraindications*; intestinal obstruction, acute intestinal inflammation, Crohn's disease, ulcerative colitis, appendicitis, and abdominal pain of *unknown origin*.
- *Other anthraquinone derivatives*; Cascara and Aloe (not used now).

Bisacodyl (Dulcolax®) (Bisadyl®)# (Minalax®)#

- Bisacodyl is *widely used* stimulant laxative.

Uses; - *Short-term* relief of *acute or intermittent* constipation.
- *Evacuation* of the bowel *before* surgery or colonic examinations.

- *Formulations*; enteric-coated tab & suppository.
- *Administration*; orally; *once daily* at bedtime.

Onset; 6-10 hours *when given* orally and *within* 30-60 minutes *when given* rectally.

- *Pregnancy*; category B.
- *Lactation*; *no data on the excretion into human milk* (safe).

Sodium Picosulfate (Picolax®)# (Dulcolax® Pico)#

- Sodium Picosulfate is a *prodrug*, *metabolised by* gut bacteria into the active compound, this compound is a *stimulant* laxative and *increases* peristalsis in gut.

Uses; - *Short-term* relief of *acute or intermittent* constipation.
- *Evacuation* of the bowel *before* surgery or colonic examinations.

- *Administration*; orally solution *once daily* at bedtime.

Pregnancy; category B (GOOD CHOICE; *in* acute cases ONLY).

Onset; 6-12 hours.

Castor Oil

- *Mechanism of action*; Castor Oil is *broken down* in the small intestine by pancreatic lipase to ricinoleic acid, which is *very irritating* to the stomach and promptly *increases* peristalsis.

Uses; *reserved* for total colonic evacuation, *such as* before to *surgery* or *radiologic* or endoscopy.

- *Administration*; orally, 16 hours *before* surgery.

Onset; 6-10 hours.

Pregnancy; *should be avoid*, it may *stimulate* uterine contractions.

Bulk Forming Laxative

- **Bulk-forming laxatives** are ***indigestible***, ***hydrophilic*** **colloids** (indigestible parts of fruits & vegetables).
- They ***absorb*** **water**, ***forming*** a **bulky, emollient gel** in the **large intestine**, *causing* **water *retention*** and **intestinal *distension***, thereby ***increasing*** **peristaltic activity**.

Psyllium or Ispaghula (Colomucil®)# (Agiolax®)# (Fybogel®)# (Meta-mucil®)#	
Wheat Bran	**Wheat Dextrin** (Benefiber®)#
Methylcellulose (Citrucel®)#	**Inulin** (Fiber Choice®)#
Polycarbophil (FiberCon®)#	

- **Wheat Bran**; is an ***insoluble*** **fiber *extracted from*** **outer shell (bran)** of **wheat grain**.
- **Wheat Dextrin**; is a ***soluble*** **fiber *extracted from*** **wheat starch**.
- **Methylcellulose** is ***not absorbed***, is a ***hydrophilic colloid***.
- **Psyllium** [SILL-i-um] or **Ispaghula** [es-PAG-ula] is a form of fiber (***insoluble*** and ***soluble***) made from the ***husks*** of the *Plantago ovata* **plant's seeds**.
- **Polycarbophil** is an ***insoluble*** **fiber**.
- **Inulin** are a group of ***soluble*** *polysaccharide* **fibers** naturally occurring by many types of plants.

Brands; # **Benefiber®** ***powder***; **odourless** and can be ***used*** on **tea** or **juice** ,
Benefiber® ***Suspension***; **apple taste**.
Colomucil®, **Fybogel®** and **Meta-mucil®** ***powder***; **Orange taste**.
Normacol® and **Agiolax®** ***powder***; **Granules *taken* directly** in the **mouth *then* drink *large* amount** of **water**.

Agiolax® granules; ***Plantago ovata*** + **Ispaghula husk** + ***Senna*** **pods**.
Onset of action; **12-72 hours**.
Uses; ***Intermittent*** or ***chronic*** **constipation**.
- ***Effectiveness***; - ***Least effective*** **laxatives**.
- ***Requires*** **adequate water intake** to be ***effective***.
- ***Less effective*** in **drug-induced constipation** & **slow-transit constipation** (STC).

Safety; ***Safe*** in **renal** and **hepatic disease**, **pregnancy** and **geriatrics** (*old people*).
- ***Side effects***; May cause **gas** and **bloating**.

Osmotic Laxatives

- **Osmotic laxatives**; are **substances** that ***increases*** **osmotic pressure**, *causing* **fluid *accumulation***, **colon *distension***, ***soft*** **stools**, and ***stimulates*** a **bowel movement**.

Glycerin (Glycerine®)

- **Glycerin** is *usually* **administered** as ***suppository*** and ***exerts*** its ***effect*** by ***irritating*** the **lining** of the **intestine** and **osmotic action** in the **rectum**.

Onset of action; *within* **30 minutes**.
Uses; ***acute*** or ***intermittent*** **constipation**.
Glycerin is considered a ***safe laxative***, can be used in **pediatric patients**.

Lactulose (Duphalac®)# (Lactulose®)

Lactulose is a ***non-absorbable*** **disaccharide** (**Galactose** and **Fructose**) that is **used *orally*** or ***rectally*** in **constipation** & **hepatic encephalopathy** (reduce ammonia levels).
- ***Mechanism***; **Lactulose** is ***metabolized by*** **colonic bacteria** to low-molecular-weight acids (**Lactic**, **Formic** and **Acetic**) resulting in an **osmotic effect** & ***lowers*** the **pH** and ***increases*** **colonic *peristalsis***.

Lactulose is considered a ***safe laxative***, can be used in **pregnancy**.
Onset of action; **1-2 days** (may require multiple doses).
Uses; - ***Intermittent*** and ***chronic*** **constipation**, ***preferred*** in **chronic liver disease**.
- It ***may*** use for ***acute*** **constipation** or in ***patients*** with an ***inadequate*** **response** to ***increased*** **dietary fiber** and **bulking agents**.
- ***Side effects***; **nausea** and **abdominal discomfort** (**gas** or **bloating**).

Saline Osmotic Laxatives

- **Saline osmotic laxatives** or **saline cathartics** are ***non-absorbable*** **salts**, which produce their effects primarily by **osmotic action**, *causing* **fluid** ***accumulation***, **colon** ***distension*** and ***stimulates*** a **bowel movement**.

Sodium Phosphate	Magnesium Citrate
Magnesium Hydroxide	Magnesium Sulfate

- **Laxel**® Sachet (**Sodium Phosphate** + **Magnesium Sulfate** + **Disodium phosphate**).
Onset of action; 0.5-3 hours (oral), 2-15 minutes (rectal).
Uses; **Acute constipation**, ***preoperative*** or ***pre-procedure*** **bowel preparation**.
- ***Contraindications***; **renal impairment**, **heart failure** and **cirrhosis**.
- ***FDA warning***; **patients** who ***received oral*** **Sodium Phosphate** for **bowel preparations** to **colonoscopy** *can development* of ***acute*** **phosphate nephropathy**.
- **Magnesium hydroxide** ***provides additional*** **bulk** and **stimulates** ***increased*** **contractions**.

Stool Softeners (Emollient Laxatives or Surfactants)

- **Stool Softeners** (**Emollient Laxatives** or **Surfactants**) are ***anionic surfactants*** that become ***emulsified*** with the **stool** *produce* ***softer*** **feces** and ***ease*** **passage**.

Docusate (Egycusate®)# (Minalax®)#

Docusate or **Dioctyl Sodium Sulfosuccinate** is a ***stool softener***. It works by helping **fat** and **water** *into the* **stool mass** to ***soften*** the **stool** (***emulsified*** **stool**).
- **Docusate** ***typically*** comes in the form of a **Sodium**, **Calcium** or **Potassium** ***salts***.
- ***Onset of action***; 1-3 days (oral), 5-20 minutes (rectal).
- ***Uses***; ***prophylaxis*** *rather than* **acute treatment**; ***Prevention*** of **opioid-induced constipation** (in combination with **Senna**) or ***prevention*** of **straining** in **post-myocardial infarction**, **postsurgical**, and **pregnant patients**.
- **Stool softeners** ***requires*** **adequate water** ***intake*** to be **effective**.
- **Stool softeners** ***should not*** be **taken** ***concomitantly with*** **Mineral Oil** *because* of the ***potential for absorption*** of the **Mineral Oil**.

Lubricant Laxatives

- **Lubricant laxatives** are ***substances*** that ***coat*** the **stool** and ***facilitating*** the **passage** of **hard stools**.

Mineral Oil

- **Mineral Oil** or **Paraffin Oil** is a ***clear***, ***viscous oil*** *derivative* of **petroleum** that ***lubricates*** **faecal material**, ***retarding*** **water absorption** *from* the **stool**.
- **Mineral Oil** may be ***given*** **orally** or **rectally**.
- ***Warning***; **Mineral Oil** *should be* ***taken*** **orally** in an **upright position** to ***avoid*** its **aspiration** and ***potential for*** **severe lipid pneumonitis**.
- ***Long-term*** **use** can *impair* **absorption** of **fat-soluble vitamins** (A, D, E, K).

Drugs for Irritable Bowel Syndrome (IBS)

- **Irritable Bowel Syndrome** (**IBS**); is a **functional** (*not* structure) **GI disorder** ***characterized by*** **abdominal pain** and **altered bowel habits** in the ***absence*** of a **specific** and **unique** ***organic pathology***.
- **IBS** ***divides into*** the *following subtypes*;
  - **Diarrhea** *predominant* (**IBS-D**).
  - **Constipation** *predominant* (**IBS-C**).
  - **Mixed IBS** (**IBS-M**) or **Alternating IBS** (**IBS-A**); *features* of ***both*** **IBS-D** & **IBS-C**.
  - **Unclassified** (**IBS-U**).
- ***N.B.***; **Post-Infective syndrome** has consequently been ***termed*** "**Post-Infectious IBS**" (**IBS-PI**).
- ***Symptoms***; - ***In addition*** to **diarrhea** and/or **constipation**, **abdominal pain** is often a **component** of ***all subtypes***.
  - ***Other symptoms***; **bloating**, **distension**, **spasm** and **urgency**.
- ***Drugs for*** **Irritable Bowel Syndrome** (**IBS**);

Antispasmodics

- ***Antispasmodics***: Used mostly for ***short-term relief*** of **abdominal pain** ***but*** *may also* ***treat*** **diarrhea** in *patients with* **IBS-D**.

Atropine

- **Atropine** is a ***prototype*** of ***antimuscarinic agents***.
- ***Peripheral*** and ***central*** (***tertiary amine***) ***effect***.
- ***Uses***; 1) **Ophthalmologic**; **Cyclopentolate** and **Tropicamide** ***more preferred***.
  2) **Gastrointestinal**
     - ***Antispasmodic***; **Hyoscine N-Butylbromide** ***more preferred***.
     - **Peptic ulcer**; **Pirenzepine** and **Telenzepine**; ***more selective*** but ***rarely*** **used**.
  3) **Urinary**; **Oxybutynin** and **Solifenacin** ***more selective***.
  4) **Cardiovascular**; **bradycardia** and **AV heart block**; ***still used*** (***highly effective***).
  5) **Respiratory**;
     - **Pre-anesthetic medication**; ***still used and*** **Glycopyrrolate** ***more preferred***.
     - **Asthma** and **COPD**; **Ipratropium** and **Tiotropium** ***more selective***.
  6) **Cholinergic Poisoning/Organophosphate Poisoning**; **DRUG OF CHOICE**.
  7) **Central Nervous System**;
     - **Parkinson's disease (Adjuvant therapy)**; **Benztropine** ***more selective***
     - **Motion sickness**; **Scopolamine** **DRUG OF CHOICE**.
- ***Common side effects***; **dry mouth**, **blurred vision**, **tachycardia**, **urinary retention** & **constipation**.

Dicyclomine or **Dicycloverine** (Spasmorest®)	**Hyoscine N-Butylbromide** (Buscopan®)
Drotaverine (Do-Spa®)#	**Tiemonium Methylsulfate** (Visceralgine®)#
Clidinium (Librax®)#	**Peppermint Oil** (Colpermin®)#

- **Hyoscine butylbromide** (**Buscopan®**); ***most popular antispasmodic drug***.
- **Tiemonium Methylsulfate** (**Visceralgine®**); ***now*** is the ***most widely*** **used**.

Dicyclomine ***should not*** be used *during* **lactation**; *may cause* **baby** ***convulsions***.

- **Librax®**; **Clidinium** + **Chlordiazepoxide** (*benzodiazepine derivative;* **Anxiolytics**); ***used*** for ***short-term relief*** to **reduce** the **abdominal pain** in **irritable bowel syndrome (IBS)** (in some patient if comorbid anxiety exists); ***Long-term*** **use** may cause **dependence** and **tolerance**. ***Side effects***; **anticholinergic side effects**. **Warnings**; Concomitant use of **benzodiazepines** (*including* **Librax®**) and **opioids** may result in **sedation**, **respiratory depression**, **coma** and **death**.
- ***Side effects***; **anticholinergic** ***side effects***.

Peppermint oil; may ***worsen*** **GERD** *but may* ***improve*** **symptoms** in **IBS**.

Mebeverine (Duspatalin®)# (Coloverin®)# (Colona®)

- Mebeverine is an *antispasmodic drug* *without* anticholinergic *side-effects* (this relieves painful muscle spasms of the gut, without affecting its normal motility).

It *used* to reduce the abdominal pain in irritable bowel syndrome (IBS).

Brands;

Duspatalin® & Coloverin® 135; Mebeverine 135 mg; 3 *times* daily, 20 min. *before* meal.

Coloverin® SR 200; Mebeverine 200 mg 2 *times* daily 20 min. *before* meal.

Coloverin®-A; Mebeverine 135 mg + Chlordiazepoxide (*Anti-anxiety*) 5 mg; 3 *times* daily, 20min. *before* meal.

Coloverin®-D; Mebeverine 135 mg + Dimethicone (*Antiflatulent*) 40 mg; 3 *times* daily, 20min. *before* meal.

Pinaverium (Spasmopinaver®)#

Pinaverium is an *antispasmodic drug* acts as a calcium channel blocker.

Trimebutine (Gast-Reg®)#

Trimebutine is an *antispasmodic drug* that *regulates* intestinal and colonic motility and *relieves* abdominal pain with antimuscarinic and *weak* μ opioid agonist *effects* in IBS.

Tricyclic Antidepressants

Tricyclic Antidepressant; Used to *relief* pain, *improve* global symptoms, and *slow* motility in *patient with* IBS-D, *but can* be used in IBS-C *but* may *worsen* constipation, *especially if comorbid* depression or anxiety exists.

Imipramine (Tofranil®)#	Amitriptyline (Tryptizol®)#	Nortriptyline (Pamelor®)#

- Imipramine, Amitriptyline and Nortriptyline are the *most studied*.
- *Actions in IBS*; at doses *sub-therapeutic* for antidepressive actions.
  - *Increases* pain threshold in the gut (providing a visceral analgesic effect).
  - *Delayed* gastric emptying and *decrease* stool frequency.
- *Precautions*; anticholinergic effects, sedation, CV effects & drug interactions.

Selective Serotonin Reuptake Inhibitors (SSRIs)

Selective Serotonin Reuptake Inhibitors (*SSRIs*); Used to *relief* pain, *improve* global symptoms, *similar to Tricyclic Antidepressant*. *Used for* *both* IBS-D and IBS-C.

Fluoxetine (Prozac®)#	Sertraline (Lustral®)#	Paroxetine (Seroxat®)#
Citalopram (Cipram®)#	Escitalopram (Cipralex®)#	

- Fluoxetine, Sertraline, Paroxetine, Citalopram & Escitalopram; *all* *viable* options.

Probiotics

- Probiotics *improve* global symptoms, bloating and flatulence.

Antiflatulent Drugs

Simethicone (Disflatyl®)#	Charcoal (Eucarbon®)#	Herbal Volatile Oil

Disflatyl®; 1-2 tab *chewable* 4 times daily or *after* meals and *before* bed.

Digestive Drugs

Digestive Enzymes or Zymogen (Digestine®)# (Spasmo-digestin®)# (Digenorm®)#

Dose; 1-2 tab 3 *times* daily, *immediately before* meals.

Spasmo-digestin®; Dicyclomine *should not* be used during lactation; *Convulsions*.

Probiotics (Lacteol® forte)# (ChocBalls®)

Stimulation of the *intestinal* flora which *increase* digestibility.

- *N.B.*; Sulpiride (Dogmatil®) is an *atypical antipsychotic* some physicians can prescribe it for *some* IBS patients; relief abdominal pain, anxiety, depression and correct stool.

Drugs for IBS-C

Laxatives

- **Laxatives** *was* **discussed** in the ***previous topic***.
Psyllium has ***best evidence***; however, it may cause **bloating** and **gas formation**.
Avoid **stimulant laxatives** because they may ***worsen*** **abdominal pain**.

Chloride Channel Activators

Lubiprostone (Amitiza®)# (Amiprostone®) (Lupicont®)

- **Lubiprostone** it is a ***derived from*** **Prostaglandin** E_1.
- ***Used*** in **Irritable Bowel Syndrome** *with* **Constipation** (**IBS-C**) in **women** ≥18 years.
- ***Most common side effects***; **nausea**, **diarrhea**, **headache** and **abdominal pain**.

Serotonin Agonists

Tegaserod (Zelmac®)# (Tegsoran®) (Zeltrod®)

- **Tegaserod** is a **5-HT_4 partial agonist** in the **enteric nervous system** (**ENS**) in the **GIT**, which ***stimulates*** **GI motility**. ***Used*** for **IBS-C**.
- ***Efficacy***; ***Improves*** **pain**, **global symptoms**, and **motility**.
It is ***removed*** from the market in 2007 due to FDA concerns about possible ***increased risks*** of **heart attack** (In **US** **Tegaserod** is ***available only*** on an **emergency-use**).

Mosapride (Fluxopride®)# (Gerdcare®)

- **Mosapride** is a **5-HT_4 partial agonist** and ***indirectly*** as a **parasympathomimetic** (***increase*** **ACh release**); ***gastroprokinetic agent***.
- It is ***used*** for the treatment of **irritable bowel syndrome** with **constipation** (**IBS-C**).
Drug interaction: **LMEIs** (e.g. **Erythromycin**) ***may cause*** ⇨ **QT interval** ***prolongation***.

Prucalopride (Resolor®)# (Prucasoft®) (Constipride®)

- **Prucalopride** is a **5-HT_4 agonist**, it is ***used*** for **Chronic Idiopathic Constipation** (**CIC**).

Guanylate Cyclase-C Agonists

Linaclotide (Linzess®)

- ***Used*** in **Irritable Bowel Syndrome** *with* **Constipation** (**IBS-C**)

Drugs for IBS-D

Antibiotics

A ***short course*** (10–14 days) of **non-absorbable antibiotic** (**Rifaximin**) may ***improve*** **global symptoms** of **IBS**, ***especially*** **bloating** in **IBS-D**.

Antimotility Agents

- **Antimotility Agents** *was* **discussed** in the ***previous topic***.

Loperamide (Imodium®)#	Diphenoxylate/Atropine (Lomotil®)#

- **Loperamide** and **Diphenoxylate** is an **opioid drug**, act as **μ receptor** ***agonist***.
- May be used as an ***adjunct*** to **other therapies** in **IBS-D**.
Contraindications; ***high*** **fever**, ***bloody*** or ***black*** **stool** and in **children > 2 years**.

Serotonin Antagonists

Alosetron (Lotronex®)	Cilansetron (Calmactin®)

- **Alosetron** and **Cilansetron** are **5-HT_3 receptor antagonist** ***used*** for the management of severe **irritable bowel syndrome** with **diarrhea** (**IBS-D**).
- **Alosetron** ***used only*** in **women**, ***but*** **Cilansetron** effective in **men** as well as **women**.
- ***Side effects***; **Alosetron**; ***serious*** (***life-threatening***) **constipation** e.g. **ischemic colitis** *may lead to* **obstruction**, (**Cilansetron** is **constipation**, ***less*** or ***self-limited***).

Drugs for Inflammatory Bowel Disease (IBD)

- **Inflammatory Bowel Disease** (**IBD**); is a ***group of*** **inflammatory conditions** of the **colon** and **small intestine**.
- ***Two major types*** of **IBD** are **ulcerative colitis** (**UC**) & **Crohn's disease** (**CD**).
- **Ulcerative colitis** (**UC**), which is ***limited to*** the **colon** and **rectum**.
- **Crohn's disease** (**CD**); which can ***affect any segment*** of the **GIT** *from the* **mouth** *to the* **anus**.
- ***Common*** **symptoms** in **both diseases** (**UC** and **CD**) *include*;
  - **Fever**.
  - **Abdominal pain**.
  - **Diarrhea** (*may be* **bloody**, **watery** or **mucopurulent**).
  - **Rectal bleeding**.
  - **Weight loss**.

➢ **Medications Used to Treat IBD:-**

Aminosalicylates

- **Aminosalicylates** was the ***first agents*** used to **treat IBD**.
- **Aminosalicylates** are drugs that ***contain*** **5-aminosalicylic acid** (**5-ASA**).
- **Used** for; 1) ***Induction*** of **remission** (relieve symptoms and inflammation).
  2) ***Maintenance*** of **remission** (prevent the disease from becoming active again).
- **Aminosalicylates** are ***believed*** to **work** ***topically*** (not systemically).

Azo Compounds

Sulfasalazine (Azulfidine®)#	**Balsalazide** (Colazal®)	**Olsalazine** (Dipentum®)

Sulfasalazine is a ***prototype agent***, *cleaved by* **colonic bacteria** to the **active portion** (**5-ASA**) and the ***inactive*** **carrier** molecule **Sulfapyridine**.
Balsalazide and **Olsalazine** are ***non- sulfa azo compounds***.
- ***Efficacy***; ***best*** in **colonic disease** (because of the colonic activation of the drug).
Mechanism of action; ***Inhibits*** **prostaglandin** and **leukotriene synthesis** (*local* anti-inflammatory).
- ***Dose***; - **Sulfasalazine**; 4–6 g/day for induction and 2–4 g/day for maintenance.
  - **Olsalazine**; 1–3 g/day. **Balsalazide**; 2–6.75 g/day.
Side Effects (dose-related); **GI disturbance**, **headache**, **arthralgia** and **folate malabsorption**.
Contraindications; **Sulfasalazine** is ***avoid*** in *patients with* a **sulfa allergy**.
- ***Monitoring/Follow-Up***; **folate supplements**, **Renal function**, **CBC** & **creatinine level/3-6 months**.

Mesalamine Compounds

Mesalamine

(Pentasa®)# (Rowasa®) (Canasa®) (Delzicol®) (Asacol® HD) (Lialda®) (Apriso®)

Mesalamine is ***designed to*** *deliver* **5-ASA** to ***different*** **segments** of the **small** or **large intestine**.
In general; ***better*** **tolerated** than **Sulfasalazine**; *considered* ***first line*** in ***mild-moderate*** **Ulcerative colitis** (**UC**) and **Crohn's disease** (**CD**).

- ***Formulations***; **Product** ***selection*** *depends on* **location** of **disease**.

Product	Formulation	Daily Dosage (g)	Site of Action
Pentasa®	Timed-release microgranules	2-4	- Small intestine - Colon
Delzicol®	Delayed-release capsules	1.6-4.8	- Distal ileum - Colon
Asacol®	Delayed-release resin (dissolves at pH >6-7)		
Apriso®	Enteric-coated granules in a delayed-release polymer matrix (dissolves at pH >6-7)	0.375-1.5 once	- Colon
Lialda®	Delayed-release Multi Matrix (MMX) System tablet (dissolves at pH >6-7)	2.4-4.8 once	- Colon
Canasa®	Suppository	1	- Rectum
Rowasa®	Enema	4	- Rectum - Terminal colon

Antibiotics

Ciprofloxacin (Cipro®)#	**Metronidazole** (Flagyl®)#

- The ***most commonly*** used agents (alone or in combination) are:
  - # **Metronidazole**; 500-750 mg orally 3 every 8 hours.
  - # **Ciprofloxacin**; 500-750 mg orally every 12 hours.

Indications of **antibiotics** in **IBD**;
- # ***Adjunctive*** **treatment** *along with* ***other*** **medications** for **active CD**.
- # **Treatment** for ***complications*** in **CD** (e.g.; **fistulas**, **perianal disease**).
- # **Prophylaxis** of **CD** ***recurrence*** in **post-operative patients**.

- **Note**; that **antibiotics** ***do not*** have a **role** in the **management** of **UC**.

Glucocorticoids

Prednisone (Hostacortin®)#	**Prednisolone** (Hostacortin-H®)#
Methylprednisolone (Depo-Medrol®)#	**Hydrocortisone** (Solu-Cortef ®)#
Budesonide (Entocort®)#	

Corticosteroids are ***rapid-acting*** **anti-inflammatory agents**.
Efficacy; are indicated ***only*** for **acute flares** (*no* role in the maintenance of remission).
Corticosteroids are ***not useful*** for ***maintaining*** **disease remission**.
- ***Administration***; by ***various*** **routes** *depending on* the **location** and **severity** of **disease**;
  - **IV**; **Methylprednisolone** (15-48 mg/day)
    Hydrocortisone (100 mg every 8 hours).
  - **Orally**; **Prednisone** (20–60 mg/day)
    Prednisolone (20–60 mg/day)
    Budesonide (9 mg/day)
  - **Topically**; Enema, suppository or foam preparations.

Side effects; **adrenal suppression**, **glucose intolerance**, **hypertension**, **sodium/water retention**, **osteoporosis**, **cataracts**, and **impaired wound healing**.

Immunomodulators

6-Mercaptopurine (6-MP) (Purinethol®)# | **Azathioprine (AZA)** (Imuran®)#

Methotrexate (MTX)

Immunomodulators have a ***slower*** **onset** (> 3 months); ***not used for*** **induction** of **remission**.

Efficacy; Used for **maintenance of remission** in **patients** ***intolerant*** of or ***not responsive*** to **Aminosalicylates**.

- ***Doses***;
  - **Azathioprine**; 2–2.5 mg/kg/day orally.
  - **Mercaptopurine**; 1–1.5 mg/kg/day orally.
  - **Methotrexate**; 15–25 mg/week intramuscularly (Crohn's disease only).

Side effects; **Bone marrow suppression, anemia, nausea, diarrhea, rash** and **hepatotoxicity**.

Folate ***supplementation*** *reduces* the **risk** of these events *without* **impairing** the **anti-inflammatory action**.

Biologic Agents

TNF-α Inhibitors

Tumor necrosis factor alpha (**TNF-α**) is a ***pro-inflammatory cytokine***.

5 TNF inhibitors; **Etanercept**, **Infliximab**, **Adalimumab**, **Certolizumab** and **Golimumab**.

####### Anti-TNF PRECAUTIONS #######

Risk of **serious infections**, or ***history of*** **recurring infections**; **black box warning**.

Recent malignancies; *especially* **lymphoproliferative cancer**; **black box warning**.

Congestive heart failure (**CHF**); New York Heart Association (NYHA) class III or IV heart failure

Demyelinating diseases; *like* **multiple sclerosis**.

Avoid **vaccination** *with* **live vaccines**.

Infliximab (Remicade®)#

- **Infliximab** is a ***recombinant*** **DNA-derived** **chimeric** **human-mouse** **IgG_1 monoclonal antibody**.
- ***Efficacy***; - **Maintenance of remission of moderate–severe CD** and **UC**.
  - **Perianal fistulizing CD**.
- ***Dose***; IV Infusion, 5 mg/kg as single dose, followed by 5 mg/kg at 2 and 6 weeks, then every 8 weeks as maintenance. (Patients losing response with time may be treated with a 10-mg/kg dose).
- **Infusion site reactions** ***may*** **occur** and may ***correlate with*** **anti-infliximab antibodies** ***formation*** (antihistamines may prevents some of these reactions).

Adalimumab (Humira®)#

- **Adalimumab** is a ***recombinant*** ***fully*** **human IgG_1 monoclonal** ***antibody***.
- ***Efficacy***; **Maintenance of remission of moderate–severe CD** and **UC**, in **patients** ***unresponsive*** to **conventional therapy**; also *indicated for* **patients** who **no longer** *respond to* **Infliximab**.
- ***Dose***; Induction; 160 mg SC on day 1 (given as four separate 40-mg injections) or two 40-mg/day injections for 2 consecutive days, followed by 80 mg SC 2 weeks later (day 15). Then, can decrease dose to 40 mg SC every 2 weeks starting on day 29 of therapy.

Certolizumab Pegol (Cimzia®)#

- **Certolizumab** is a ***unique*** **TNF-α blocker** that contains a ***recombinant***, ***humanized*** **antibody Fab fragment** ***conjugated to*** a **Polyethylene Glycol** (**PEG**) (not contain **IgG_1**) with ***specificity*** for ***human*** **TNF-α**.
- ***Efficacy***; **Maintenance of remission of moderate–severe CD**, in **patients** ***unresponsive*** to **conventional therapy**.
- ***Dose***; 400 mg **SC** initially and repeat at weeks 2 and 4, followed by 200 mg every other week or 400 mg every 4 weeks.

Golimumab (Simponi®)#

- **Golimumab** is a ***human*** **monoclonal antibody** with a ***high*** **affinity** for ***soluble*** and ***membrane-bound*** **TNF-α**.
- ***Efficacy***; **Maintenance of remission of moderate–severe UC**, in **patient's** ***unresponsive*** to in **previous therapies** or ***requiring*** *continuous* **steroid therapy**.
- ***Dose***; 200 mg subcutaneously at week 0, then 100 mg at week 2, then 100 mg every 4 weeks.

Anti-integrin Agents

Natalizumab (Tysabri®)#

Natalizumab is a ***humanized*** **monoclonal antibody** ***against*** the **α-4 subunit of integrin molecules** (*leukocytes*), ***used*** in the ***treatment of*** **multiple sclerosis** & **Crohn's disease**.

- ***Efficacy***; **Maintenance of remission of moderate–severe CD**, in **patients** ***unresponsive*** to **conventional therapies** and **TNFα** ***inhibitors***.
- ***Dose***; 300 mg IV infusion over 1 hour every 4 weeks, the treatment cost is very expensive.
- ***Precautions***; **Progressive Multifocal Leukoencephalopathy**; **PML** (viral CNS infection, John Cunningham virus; JCV); rapidly progressive and usually results in death or permanent disability;
  - The ***risk of PML***;
    1) History of previous immunosuppression.
    2) Long duration of **Natalizumab** treatment, beyond 2 years.
    3) JC virus antibody positivity.

Vedolizumab (Entyvio®)#

- **Vedolizumab** is a ***humanized*** **monoclonal antibody** ***against*** the **α4β7-integrin of integrin molecules** (*leukocytes*).
- ***Efficacy***; **Maintenance of remission of moderate–severe CD** and **UC** in **patients** ***unresponsive*** to **conventional therapies** and **TNFα** ***inhibitors***.
- ***Dose***; 300 mg IV given at 0, 2, and 6 weeks, then given every 4 weeks. Discontinue if no evidence of improvement at 14 weeks.
- ***Precautions***; similar to that of **Natalizumab**, ***but*** with ***lower risk*** of **PML**.

➢ Pancreatic Enzyme Replacement Therapy (PERT):-

- ***Exocrine* pancreatic insufficiency** is ***most commonly*** *caused by* **cystic fibrosis, chronic pancreatitis** or **pancreatic resection**.
- *If* **secretion** of **pancreatic enzymes** *below* **10%** of **normal**; **fat** and **protein *digestion*** is ***impaired*** & can lead to **steatorrhea, azotorrhea, vitamin malabsorption** & **weight loss**.
- The **Pancreatic Enzyme Products (PEPs)** or **Pancrelipase *used in* PERT** are *extracts of* **porcine pancreas** that contain ***all* 3 pancreatic enzymes (amylase, protease** and **lipase)** in ***varying proportions***, are ***used for* pancreatic enzyme insufficiency**.
- The are **6 PEPs** have been ***approved*** by the **US FDA**;

Pancreatic Enzyme Products (PEPs) or Pancrelipase

Brand	Lipase (units)	Amylase (units)	Protease (units)	Formulation
Creon®	3000	15,000	9500	Capsules with enteric-coated microspheres
	6000	30,000	19,000	
	12,000	60,000	36,000	
	24,000	120,000	76,000	
	36,000	180,000	114,000	
Viokace®	10,440	39,150	39,150	Immediate-release tablet
	20,880	78,300	78,300	
Pertzye®	8000	30,250	28,750	Capsules with enteric-coated microspheres
	16,000	28,750	57,500	
Zenpep®	3000	16,000	10,000	Capsules with enteric-coated beads
	5000	27,000	17,000	
	10,000	55,000	34,000	
	15,000	82,000	51,000	
	20,000	109,000	68,000	
	25,000	136,000	85,000	
	40,000	218,000	136,000	
Ultresa®	13,800	27,600	27,600	Capsules with enteric-coated mini-tablets
	20,700	41,400	41,400	
	23,000	46,000	46,000	
Pancreaze®	2600	10,850	6200	Capsules with enteric-coated micro-tablets
	4200	17,500	10,000	
	10,500	43,750	25,000	
	16,800	70,000	40,000	
	21,000	61,000	37,000	

- ***Dosing***; based on **lipase content** (units) in the product;
  - ***Initial***; 500 units/kg/meal.
  - ***Dose range***, 500-2500 units/kg/meal.
  - ***Maximum dose***; 10,000 units/kg/day.
  - ***Usually adult doses***; 30,000–40,000 units/meal, with one-half dose for snacks.
- ***Administration***; orally before or during meal.
- ***Dose monitoring***; ***increased*** in **weight gain** and ***decreased*** in **steatorrhea**.
- ***May need*** to ***add* proton pump inhibitors (PPIs)**; *if* **maximal response** is ***not seen***.
- ***Side effects***;
  - **Nausea** or **abdominal cramping**.
  - **Allergy** in patients with *pork allergy*.
  - **Hyperuricosuria, hyperuricemia**.
  - **Fibrosing colonopathy** (generally seen with doses greater than 10,000 units/kg/day)
- ***Pregnancy***; **category C**.

Gallstones

- **Bile** is a ***complex*** of **fluid** *containing* **water, electrolytes** and ***organic molecules*** *including* **bile acids, cholesterol, phospholipids** and **bilirubin**.
- ***Bile Function***; - **Bile acids**, ***help for*** **digestion** and **absorption** of **fats** and **fat-soluble vitamins** in the **small intestine** (*by acting as a surfactant that emulsifies them into micelles*). *Many* **waste products**, *including* **bilirubin**, are *eliminated from* the **body** by ***secretion*** into **bile** and *elimination in* **feces**.
- **Gall bladder** ***stores*** and ***concentrates*** **bile** and **cholesterol** is ***soluble*** in **bile**.
- **Gallstone** (**Cholelithiasis**); is a ***stone formed within*** **gallbladder**, *about* **80%** of **patients** are ***asymptomatic***.
- **Gallstones**, ***most of which*** are **composed** *predominantly of* **cholesterol**.
- **Gallstones** ***develop*** when **bile** *contains* ***too much*** **cholesterol** and ***not enough*** **bile salts**.
- ***Common Symptoms***; **biliary colic** (**crampy pain**; ***right*** **upper abdominal pain**, *usually* ***after*** **heavy meals** and ***lasts*** **1-4 hours**), ***more than*** **5 hours** → **Complication**.
- **Complications**; **cholecystitis, cholangitis** and **acute pancreatitis**.
- ***Complication signs***; **biliary colic** ***more than*** **5 hours, fever**, ***persistent*** **tachycardia, hypotension** and **jaundice** (yellowish skin).
- **Surgery**; ***rapid*** **treatment** of **complications** is **cholecystectomy** (**gallbladder** ***remove***).
- ***Medical treatments*** of **asymptomatic gallstones** is **oral bile salt** (**Ursodeoxycholic acid**);

Ursodeoxycholic Acid or Ursodiol (Ursofalk®)# (Livagoal®) (Ursogall®)

Ursodeoxycholic Acid (**UDCA**) or **Ursodiol** is a ***naturally occurring*** **bile acid** found in *small quantities* in *normal* **human bile** and in ***larger quantities*** in the **bile** of *certain species* of **bears**.

Mechanisms; 1) **Ursodiol** ***regulate*** **cholesterol** by;

* ***Reducing*** **intestinal cholesterol** ***absorption***.

* ***Reducing*** **hepatic cholesterol** ***synthesis*** and ***secretion***.

2) **Ursodiol** is a **hydrophilic bile acid** that ***solubilizes*** **cholesterol** and ***promotes*** its **dispersion** in **aqueous fluids**, ***reducing*** **viscosity** and ***improving*** **bile flow**.

- ***From 1 and 2***, ***results***; **Ursodiol** *reduces* **cholestasis**, ***prevents*** **formation** and ***promotes*** **dissolution** of **cholesterol-containing gallstones**.

Indications; **Cholelithiasis, Primary Biliary Cholangitis** (**PBC**), **Cholestasis** (slowing or stopping of bile flow) in **cystic fibrosis, new-born infants** and **pregnant women** (relieve itching).

- **Chenodeoxycholic Acid** (**Chenodiol**) is an ***epimer of*** **Ursodeoxycholic Acid**, ***but*** have ***potential*** **hepatotoxicity** and ***poor*** **response**.

Rowachol®#

#**Rowachol®** ***contains*** **essential oils** (**Pinene, Camphene, Cineol, Menthone, Menthol, Borneol**) that ***may help*** to ***dissolve*** or ***break up*** **cholesterol-based gallstones**.

Appendicitis

- **Appendicitis** is ***inflammation*** of the **appendix**.
- **Appendix** is a **tube** ***of*** **tissue** that ***extends from*** **large intestine**.
- There is ***no accurate*** **function** of **appendix** and we ***can*** **live** ***without*** **it**.
- **Appendicitis symptoms**; ***right*** **lower abdominal pain**, **nausea, vomiting** and ***decreased*** **appetite**.
- ***Severe complications***; **ruptured appendix**; ***painful inflammation***, **sepsis** (pus-filled abscess) and can be **fatal**.
- ***All cases*** of **appendicitis** are treated as **emergencies**, ***requiring*** **surgery** (**appendectomy**).
- **IV antibiotics** are used to ***delay*** or ***avoid*** the **onset of sepsis**.

Respiratory

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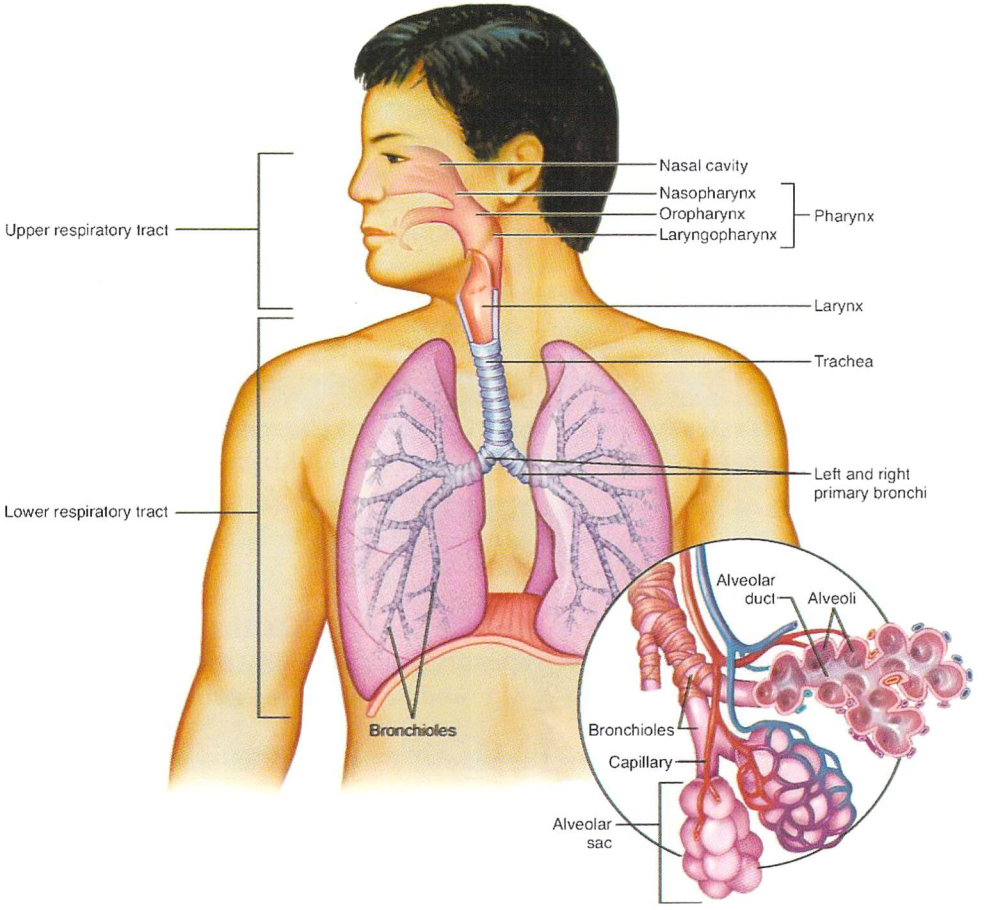

Antihistamines

- **Histamine** is formed by ***decarboxylation*** of the amino acid **L-histidine**, a reaction catalyzed by **histidine decarboxylase enzyme**.
- ***Once formed***, **Histamine** is either **stored *or rapidly* inactivation**.

Histamine *Storage*:

* ***Tissues***; It is found in ***most*** tissues but is present in ***high*** conc. in the **lungs**, **skin** and **fundus** of the **stomach** (Enterochromaffin-Like; ECL cells).

* ***Cells***; It is found largely in **mast cells** and **basophils**.

* ***Neurons***; Histaminergic neurons in the **brain**.

Histamine *Release*;

A) Immunologic Release:

- **Hypersensitivity reaction (Type I) (immediate hypersensitivity)**: **Antigen** (***allergen***) react with **antibody (IgE)** on the mast cell ⇨ these reaction increase release of histamine from mast cells.

B) Chemical and Mechanical Release;

- **Morphine** and **Tubocurarine**, can ***displace*** **histamine** from its bound form within cells. This type of release is not associated with mast cell injury or degranulation.

- **Histamine** exerts its ***biological actions*** by combining with **specific cellular receptors** located on the surface membrane.
- **Histamine** exerts ***powerful effects*** on **smooth** and **cardiac muscle**, on certain **endothelial** and **nerve cells**, on the **secretory cells of the stomach**, and on **inflammatory cells**.

Histamine Antagonists

1) **Physiological Antagonist of Histamine**: #
   # **Adrenaline** having ***apposite*** to those **histamine** on **H_1 receptor** due to cause **bronchodilatation** (β_2) and **vasoconstriction** (α_1).
2) **Mast Cell Stabilizers** # (***Inhibit*** **histamine release**); ⇨ ***Decrease*** **histamine release** from **mast cell** ⇨ ***used as*** **prophylactics in asthma**.
   A) **Cromolyn** (or **Cromoglycate**), **Nedocromil** and **Ketotifen**.
   B) **β_2-adrenoceptor agonists** e.g. **Salbutamol**.
   C) **Methylxanthines** e.g. **Theophylline**.
3) **Histaminase Enzyme** (**Diamine Oxidase**): ⇨ ***Responsible for*** **histamine *metabolism***.
4) **Histamine Receptors Blockers**:
   A: **H_1**-receptor blockers.
   B: **H_2**-receptor blockers.
   C: **H_3**-receptor blockers.
   D: **H_4**-receptor blockers.

H_1-receptor Antagonists (Antihistamine)

The ***term*** **antihistamine** ***refers primarily*** to the classic **H_1-receptor blockers**.

- The ***new*** classification of **H_1-receptor blockers**; ***First-***, ***Second-*** & ***Third-generation***.

First Generation (Sedating Antihistamines)

The *older* **first-generation** drugs are still *widely used because*; **effective** & **inexpensive**
Most of these drugs *penetrate the CNS* (lipophilic) and *cause* **sedation**.
Short duration of action (4-6 hours); **3** ***times*** **daily**.
Some of these drugs have another actions in addition of H_1-blockers e.g. *Anticholinergic*, *Antiemetic*, *Antiserotonin* and *local anesthetic effects*.

Pheniramine (Avil®)#	**Chlorpheniramine** (Anallerge®)#
Brompheniramine (VaZol®)	**Hydroxyzine** (Atarax®)#
Triprolidine (Actifed®)#	**Clemastine** (Tavegyl®)#
Dimethindene (Fenistil®)#	**Mequitazine** (Primalan®)

Chlorpheniramine, **Triprolidine**; ***slight*** **sedation**, ***common component*** of **cold medication**.
Hydroxyzine; ***marked*** **sedation**.
- **Brompheniramine**, **Dimethindene**, **Clemastine**, **Pheniramine** & **Mequitazine**; ***slight*** **sedation**

Diphenhydramine (Dramenex®)#		**Dimenhydrinate** (Dramamine®)#
Meclizine (Navidoxine®)#	**Cyclizine** (Emetrex®)#	**Doxylamine** (Donormyl®)#
Promethazine (Phenergan®)#		**Cinnarizine** (Stugeron®)#

Diphenhydramine, **Dimenhydrinate**, **Cyclizine**, **Meclizine**, **Doxylamine**, **Promethazine** and **Cinnarizine** are the ***most effective*** agents for ***prevention*** of the symptoms of **motion sickness** and **vertigo** (***prevent*** **nausea** and **vomiting**). ***Antiemetic action***; ***due to block central*** H_1 and M_1 **muscarinic receptors**.
Cinnarizine is an **antihistamine** and **calcium channel blocker**, it is also *known to* ***promote*** **cerebral blood flow**, and so is ***used*** to ***treat*** **cerebral apoplexy**, **post-trauma cerebral symptoms**, and **cerebral arteriosclerosis**.
Diphenhydramine, **Dimenhydrinate** and **Promethazine**; ***marked*** **sedation**.
Cyclizine and **Meclizine**; ***slight*** **sedation**.
Doxylamine (**Donormyl®**)#; ***strong*** **sedation**, ***used*** in the ***treatment*** of **insomnia**.

Cyproheptadine (Triactin®)#

Cyproheptadine (**Triactin®**)# # also acts as a ***serotonin antagonist*** on the ***appetite center*** and is sometimes ***used*** *off-label* as an **appetite stimulant**; ***widely used***

Second Generation (Non-sedating Antihistamines)

The ***newer*** **second-generation** drugs are **expensive**.
They are made **polar** mainly by adding carboxyl groups, the second-generation agents ***don't pass*** **the BBB**, causing ***less*** **CNS sedation**.
Long duration of action (**12** to **24 hours**); ***once*** **daily** *at* **bed time**.
More **selective** (***no*** anticholinergic, ***no*** antiemetic and ***no*** antiserotonin activity).

Cetirizine (Zyrtec®)#	**Loratadine** (Claritin®)#	**Acrivastine** (Semprex®)
Ebastine (Kestine®)		**Mizolastine** (Zolim®)

Cetirizine is a ***partially*** **sedating** ***second-generation agents***.
- **Loratadine**, **Acrivastine**, **Ebastine** and **Mizolastine**; ***least*** **sedation**.

Ketotifen (Zaditen®)#	**Alcaftadine** (Lastacaft®)#	**Bepotastine** (Talion®)#
Emedastine (Emadine®)	**Azelastine** (Azelast®)#	**Olopatadine** (Patanol®)#

Ketotifen, **Alcaftadine**, **Bepotastine**, **Emedastine**, **Azelastine** and **Olopatadine**; ***ophthalmic formulations*** and used for the ***treatment*** of **allergic conjunctivitis**.
Azelastine and **Olopatadine** ⇨ have ***intranasal*** **formulations**.
Ketotifen ⇨ has ***oral formulations***.
Azelastine & **Ketotifen**; have **mast cell** ***stabilizing effects*** in addition to **H_1-blocking effects**.

Third Generation (Non-sedating Antihistamines)

Third-generation are the ***active enantiomer*** (**Levocetirizine**) or ***metabolite derivatives*** (**Desloratadine** & **Fexofenadine**) of ***second-generation drugs*** intended to have ***increased*** **efficacy** with ***fewer*** **adverse drug reactions**.
They are ***more*** **expensive** ***than*** **second-generation**.
Don't pass **the BBB**, causing ***no*** OR ***less*** **CNS sedation** ***than*** **second-generation**.
Long duration of action (**24 hours**); **once daily** at **bedtime**.
Pure **selective** for **H_1-receptors**.

Levocetirizine (Allear®)#	**Desloratadine** (Aerius®)#	**Fexofenadine** (Telfast®)#

Levocetirizine is the ***active enantiomer*** of **Cetirizine**, and cause ***partially*** **sedation**.
Desloratadine, **Fexofenadine**, are the ***least*** **antihistamines sedation**.
Desloratadine is an ***active metabolite*** of **Loratadine**.
Fexofenadine is an **active metabolite** of **Terfenadine**.
- **Terfenadine** (Prodrug) is metabolized to **Fexofenadine** (Active drug), liver microsomal enzyme inhibitors (e.g. Erythromycin) inhibit this metabolism, lead to ↑ concentration of Terfenadine in the blood ⇨ Block K^+ channels in the heart ⇨ cardiac arrhythmia (QT interval prolongation). (No cardiotoxicity with fexofenadine).

Pharmacodynamics;
1) **Sedation**;
A ***common effect*** of **first-generation**; ***useful*** as "**sleep aid**".
At ***very high toxic*** **dose**, marked stimulation; ***convulsions***.
2) **Antinausea and antiemetic actions**;
Several **first-generation**; **prevention motion sickness**.
3) **Anticholinoceptor actions**;
Many **first-generation**; **Diphenhydramine**, **Clemastine**, **Dimenhydrinate** and **Doxylamine** have significant **atropine-like effects** (**dry mouth**, **urinary retention** and **blurred vision**).
4) **Adrenoceptor-blocking actions**;
α_1 blocking effects can *demonstrated for* many **first-generation** ***especially*** **Promethazine**, may ***cause*** **orthostatic hypotension**.
5) **Serotonin-blocking action**;
Cyproheptadine, it is ***used*** **off-label** as an **appetite stimulant**.
6) **Local anesthesia**;
Several **first-generation** are ***potent*** **local anesthetics** especially **Diphenhydramine** and **Promethazine** they **block Na^+ channels** in ***excitable*** **membranes**.

Therapeutic Uses;
1) **Allergic Reactions**;
Allergic rhinitis (**hay fever**); **ONLY** **2nd/3rd generation**.
Urticaria & **dermatitis**; **1st generation** **sedative effects** (↓ itching).
2) **Dry Cough**; **ONLY** **1st generation** (*unknown central mechanism*); ***especially*** **Diphenhydramine**, **Promethazine** and **Chlorpheniramine**.
3) **Motion Sickness** *and* **Vestibular Disturbance**;
Scopolamine and ***some*** of **1st generation** ***especially*** **Diphenhydramine** and **Promethazine** are **most effective agents**.
Cyclizine and **Meclizine** ***also effective*** with ***less*** **sedation** *than* **Diphenhydramine**.
4) **Nausea** **and** **Vomiting of Pregnancy** (**NVP**);
Meclizine, **Cyclizine** and **Doxylamine** are ***combined with*** **V-B6**.
5) **Somnifacient** (**Hypnotic**);
- **1st generation**; especially **Doxylamine** and **Diphenhydramine**.

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Antihistaminic especially **1st generation** is *contraindicated* in the *individuals* **working** in **jobs** in *which* **wakefulness** is *critical* such as **drivers** and **worker in dangerous machines**.

Systemic Acute **Toxicity Emetrex® Ampoule**; is **NOT** *recommended* in **CHILDREN** *younger than* **6 years** to *prevent* **vomiting** (*serotonin antagonists* such as **Ondansetron** is *safer*).

H_3-receptor Antagonists

Betahistine (Betaserc®)#

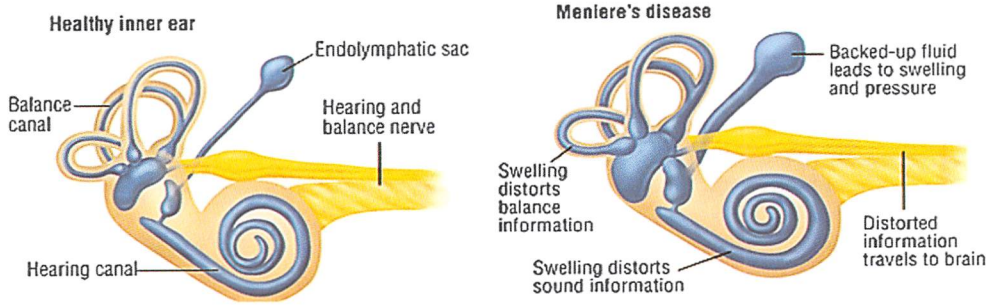
Betahistine is an **anti-vertigo** drug *used* in **balance disorders** or **relieve vertigo** symptoms associated with **Ménière's** [men-YEERS] **disease**.

Mechanism;

- **Betahistine** has a *very strong* **affinity** as an *antagonist for* **histamine H_3-receptors** and a *weak affinity* as an *agonist for* **histamine H_1-receptors**.
- **Betahistine** seems to *dilate* the **blood vessels** *within* the **inner ear** which can *relieve* **pressure** from *excess* **fluid** and act on the **smooth muscle**.

Dose; - **Betaserc® 8 mg tab; 1-2 tab 3 times daily**.
- **Betaserc®16 mg tab; ½-1 tab 3 times daily**.
- **Betaserc® 24 mg tab; 24-48 mg** *divided* **over the day** (*max dose*; **48 mg**).

- **Ménière's disease** is a disorder of the inner ear that causes spontaneous episodes of vertigo, fluctuating hearing loss, ringing in the ear (tinnitus) and affects only one ear.



Eicosanoids

- **Eicosanoids** are *oxygenation* products of **polyunsaturated long-chain (20 C atom) fatty acids**.

There are *multiple subfamilies*; **Prostaglandins (PGs)**, **Thromboxanes (TXs)** and **Leukotrienes (LTs)**.

- **Eicosanoids** are *not stored* within cells, *but* are **synthesized as required**.

Cysteinyl LTs (LTC_4, LTD_4 and LTE_4) ⇨ *bronchospasm* (**1000 times** *more potent* **than Histamine**).

Bronchospasm occur about **10%** of **people taking NSAIDs**, *because* of a *shift* in **arachidonic acid** *from* **COX** *to* **5-LOX**; **Leukotrienes** *formation*.

Asthma and COPD

Asthma; is a ***chronic inflammatory disorder*** of the **airways** *causing* ***recurrent*** **episodes** *of*; **wheezing**, **breathlessness**, **cough** and **chest tightness**, *particularly* at **night** or ***early*** in the **morning**.

Chronic Obstructive Pulmonary Disease (**COPD**); is a ***chronic*** **limitation** ***in*** **airflow** ***encompassing*** **emphysema** and **chronic bronchitis**;

1) **Chronic bronchitis**; *consists of* ***persistent*** **cough** ***plus*** **sputum production** for ***most days*** of **3 months** in ***at least*** **2 consecutive years**.
2) **Emphysema**; is ***abnormal permanent*** **enlargement** of the **airspaces distal** to the **terminal bronchioles**, *accompanied by* ***destruction of*** **their walls** and ***without*** **obvious fibrosis**.

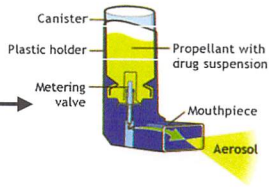
Cigarette smoking ***causes*** about **80-90%** of ***all*** **COPD cases**.

Asthma is *caused by* a ***combination*** of **complex** and ***incompletely understood*** **environmental** and **genetic** ***factors***;

- **Environmental allergens** (e.g.; house dust mites; animal allergens, especially cat and dog and cockroach allergens and fungi).
- **Viral respiratory tract infections**.
- **Aspirin** or **NSAIDs**.
- **Exercise** or **hyperventilation**.
- **Chronic sinusitis** or **rhinitis**.
- **Environmental pollutants** or **smoking**.
- **Obesity**.
- **Gastroesophageal reflux disease** (**GERD**).
- **β-blockers** (*including ophthalmic*).
- **Emotional factors** or **stress**.
- **Irritants** (household sprays or paint fumes).
- **Genetics**.

Types of Inhaler Device;

A) Metered Dose Inhalers (**MDI**) *such as* (**Ventolin®**)



- Widely available for most inhaled medicines.
- Small, easy to carry (unless used with a spacer).

B) Dry Powder Inhalers;

- **Powder** *such as*; **Turbuhaler® - Accuhaler® - Ellipta®**
- **Powder Capsules** *such as*; **Breezhaler® - Handihaler®**

C) Respimat® Device;

- Respimat are soft mist inhalers, *such as*; **Spiriva® Respimat®**

Asthma Medications

Asthma Medications are *generally* ***divided into*** **two categories**:

1) **Quick relief** (**reliever medications**); *relieve acute asthma exacerbations*;
   - **Short-acting β_2-agonists** (**SABAs**).
   - **Systemic** (**Oral**) **Corticosteroids**.
   - **Anticholinergics** (***only for severe exacerbations***).
2) **Long-term control** (**controller medications**);
   - **Inhaled Corticosteroids**.
   - **Long-acting β_2-agonists** (**LABAs**).
   - **Long-acting Anticholinergics**.
   - **Methylxanthines**.
   - **Leukotriene Modifiers**.
   - **Mast Cell Stabilizers**.

β_2-adrenoceptor Agonists

β_2-*agonists* are the ***most effective*** **bronchodilators** ***available***.

- ***In general activation*** of **β_2-adrenergic receptors** ☞
  - **Smooth muscles**; **bronchodilatation** and **uterine muscle** ***relaxation***.
  - **Skeletal muscles**; **vasodilatation** and **tremors**.
  - **Heart**; **heart muscle** ***contraction***.
  - **Mast cells**; ***inhibition*** of **mast cell** ***degranulation*** **(mast cell stabilizer)**.
  - **Metabolic**; **glycogenolysis, gluconeogenesis, lipolysis, hypokalemia & ↑ lactate.**
    - **Clenbuterol** is a **β_2 agonist** ***used by*** **bodybuilders** for **performance-enhancement** and **weight loss** **(lipolysis** and **anabolic effect)**

Side Effects; **Tremor, Tachycardia, Hypokalemia, Hypomagnesemia, Hyperglycemia.**

Short-acting β_2-adrenoceptor Agonists (SABA); Acute Asthma

Salbutamol or Albuterol (Ventolin®)#

Levosalbutamol or Levalbuterol (Chronsalbutam®)

Terbutaline (Bricanyl®)# | **Pirbuterol** (Maxair ®)

Salbutamol or **Albuterol** is the ***most commonly*** used **bronchodilator** that is ***available*** in **multiple forms** (e.g.; solution for nebulization, metered-dose inhaler, and oral solution).

- **Salbutamol** ***Dose***; ***Metered-dose inhaler*** (***MDI***); 2 puffs every 4 to 6 hours as needed. ***Inhalation capsules***; 200 mcg inhaled every 4 to 6 hours (may increase to 400 mcg inhaled every 4 to 6 hours, if necessary). ***Nebulizer***; 1.25–5 mg in 3 cc of saline every 4 to 8 hours as needed. **Tablet** and **syrup**; 2-4 mg orally every 6-8 hours (not to exceed 32 mg/day).

Long-acting β_2-adrenoceptor Agonists (LABA); Chronic Asthma

LABA ***should not*** **use** ***for*** **acute asthma**.

LABA ***used for*** **prevention** (such as; **nocturnal asthma** or **exercise-induced asthma**).

LABA ***must be*** ***used in*** **chronic asthma** in ***combination with another long-term asthma-control medicine*** (e.g. **Inhaled Corticosteroids** (**ICS**) such as **fluticasone** and **budesonide**); to ***prevent*** **ASTHMA-RELATED DEATH**.

LABA in **COPD**; ***may be*** used as **mono-therapy** *or* in **combination** with **Corticosteroids**.

Formoterol (Foradil®)# | **Salmeterol** (Serevent®)#

Formoterol and **Salmeterol** ***duration of action*** may ***extended up*** to **12 hours**.

- ***Dose***; 1 puff or 1 inhalation capsule 2 times daily.
- **β_2-Agonist/Inhaled Corticosteroid Combinations**;

Product	Corticosteroid	β_2-Agonist
# Symbicort®	Budesonide	Formoterol
# Dulera®	Mometasone	Formoterol
# Fostair®	Beclomethasone	Formoterol
# Advair® - Seretide®	Fluticasone	Salmeterol
# Breo® Ellipta®	Fluticasone	Vilanterol

- **Vilanterol** an **ultra-long-acting β_2 agonist** (**ultra-LABA**), it was ***approved by*** **FDA** in **2013** for **COPD**. In **2015**, ***approved*** **once-daily treatment** *for* **asthma** in **people ≥ 18 years**. **Breo®** **Ellipta** ***contraindicated*** in ***patients with*** **severe milk protein allergy**. **Indacaterol** is the ***first*** **ultra-LABA**, **approved** ***only*** for **long-term control** of **COPD** ***symptoms*** (***not used*** in **chronic asthma**).

Corticosteroids

Benefits of *corticosteroids* in asthma;

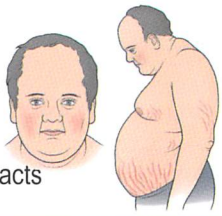
1) ***Increasing*** **number** and **sensitivity** of **β_2 receptors**.
2) ***Reducing*** **mucus** ***production*** and **hypersecretion**.
3) ***Reducing*** **airway edema** and **exudation**.
4) ***Reducing*** **bronchial hyperresponsiveness (BHR)**.

Mechanisms of *corticosteroids* in asthma;

1) ***Suppress*** **several proinflammatory cytokines** → ***reducing*** **inflammatory cell** ***activation*** and ***infiltration*** → ***decreasing*** **vascular permeability**.
2) ***Prevent*** **action** of **proinflammatory cytokines** *on the* **cell**.
3) ***Increase*** **β_2 Receptor density** (within 4 hours of corticosteroid administration) and ***improve*** **responsiveness** of **β_2-agonists** (within 2 hours of corticosteroid administration).
4) ***Reversal increased*** **BHR** (requires at least 1 week of therapy).

Side Effects of Chronic Systemic Glucocorticoid Administration;

- Hypothalamic–pituitary-adrenal suppression
- Skeletal muscle myopathy
- Aseptic necrosis of bone
- Pseudotumor cerebri
- Sodium and water retention
- Hypertension
- Impaired wound healing
- Posterior subcapsular cataracts
- Central redistribution of fat



- Growth retardation
- Osteoporosis/fractures
- Pancreatitis
- Psychiatric disturbances
- Hypokalemia/hyperglycemia
- Skin striae
- Inhibition of leukocyte & monocyte function
- Glaucoma
- Moon facies

Oral (Systemic) Corticosteroids; Acute Asthma

Prednisone (Hostacortin®)#	**Prednisolone** (Hostacortin-H®)#
Methylprednisolone (Solu-Medrol®)#	

Prednisone is a ***prodrug***; ***converted*** via *liver metabolism* to **Prednisolone** (***active***).

Oral Corticosteroids are ***used for*** **short courses** (3-10 days) to control **acute asthmatic episodes**. # ***Dose***; 40–80 mg in 1 or 2 divided doses.

Inhaled Corticosteroids (ICSs); Chronic Asthma

Beclomethasone (Beclosone®)	**Fluticasone** (Flovent®) (Flixotide®)#
Mometasone (Asmanex®)	**Budesonide** (Pulmicort® Flexhaler)# (Miflonide®)#
Triamcinolone (Azmacort®)#	**Flunisolide** (Aerospan®)

ICSs are the ***first line*** (***drugs of choice***) for ***long-term control*** ***any degree*** of **persistent asthma**.

ICS are given as ***long-term*** to ***avoid*** **adrenal insufficiency**, ***but*** **high doses** of **ICS** *may cause* **adrenal suppression**.

Onset of improvement; **5–7 days** (additional benefit may occur over several weeks).

ICS *have* ***few systemic*** **side effects** (consider **Calcium** and **Vitamin D** ***supplements*** in **adults**, particularly in premenopausal women).

ICS ***local*** **side effects**; due to **ICS** deposition on the **oral** and **laryngeal mucosa** *can cause*;

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1) **Oropharyngeal candidiasis (Thrush)**; due to local immune suppression.
2) **Hoarseness (Dysphonia)**; due to myopathy of the vocal cords.

Patients ***should be*** **gargle water** and **spit** ***after*** *each* **inhaled treatment** to ***decrease*** the **chance** of these ***local*** **adverse events**.

Ciclesonide (Alvesco®)#

Ciclesonide is *recently approved* ICS as a **prodrug** ***activated by*** **esterases** in **lung** to ***form*** its **active metabolite** (**Desciclesonide**)

Because it is ***not activated*** **until** it ***reaches*** the **lung**, **Ciclesonide** *may cause* ***fewer*** **local side effects**.

Desciclesonide is ***tightly*** **bound** to **plasma proteins**, and so has ***little*** **access** to **glucocorticoid receptors** in **skin**, **eye** and **bone**, ***minimizing*** its **risk** of *causing* ***systemic*** **side effects**.

Anticholinergics

- A ***number*** of the **triggers** and **mediators** of **asthma** (i.e., **Histamine**, **Prostaglandins**, **Sulfur dioxide**, **Exercise** and **Allergens**) ***produce*** **bronchoconstriction** in part ***through*** **vagal reflex mechanisms** (parasympathetic stimulation).
- The **anticholinergic agents** ***block*** **vagally** *mediated* ***contraction*** of **airway smooth muscle** and **mucus secretion**.

Side effects; **Headache**, **flushed skin**, **blurred vision** and **tachycardia**.

Ipratropium (Atrovent®)#

Ipratropium is a ***non-selective*** **muscarinic receptor blocker**, **quaternary ammonium derivatives** (***not cross BBB***).

Indications;

Off-label; 1) ***Acute*** **severe asthma** in **patients** ***not completely*** **responsive** to **β_2-agonists** ***alone***.

Approved; 2) **Chronic Obstructive Pulmonary Disease** (**COPD**).

- ***Onset of action***; **30–60 minutes** (**β_2-agonists**; **5–10 minutes**).
- ***Duration of action***; **4-8 hours**.
- ***Dose for Acute*** **severe asthma** (**emergency**); ***Off-label***
  - ***Metered-dose inhaler*** (***MDI***); 8 puffs every 20 min as needed for up to 3 h.
  - ***Nebulizer***; 500 mcg (1 unit dose vial) every 30 min for 3 doses, then every 2–4 h as needed.
- ***Anticholinergic combinations***; **Ipratropium** + **Salbutamol** (**Combivent®**)#
- A ***longer-acting*** **antimuscarinic agent** such as **Tiotropium** and **Aclidinium**; are ***approved*** and ***used only*** in **COPD** (***not used*** in **asthma**), ***but*** ***recently*** **Tiotropium** **studies well** in **chronic asthma** and is ***approved***; **Spiriva® Respimat** ***only***.

Tiotropium (Spiriva® Respimat)#

Tiotropium is a ***selective*** **muscarinic receptor blocker** (***mainly on*** M_3), used in ***management*** of **COPD**.

- ***Recently*** **Tiotropium** **studies well** in **chronic asthma** and is ***approved***; **Spiriva® Respimat** [inhaled spray] ***only*** is used in **chronic asthma**; **Spiriva® HandiHaler** [inhaled capsule] ***used*** in **COPD** but ***NOT used in*** **chronic asthma**.
- ***Dose for*** **chronic asthma** (**Spiriva® Respimat**); **2 puffs** ***once*** **daily**.

Methylxanthines

- The **3** ***important*** **methylxanthines** are **Theophylline**, **Theobromine** and **Caffeine**.
- The ***importance*** of **Theophylline** as a ***therapeutic agent*** in the ***treatment*** of **asthma** and **COPD**.

- **Aminophylline** is a **Theophylline** ***complex with*** **Ethylenediamine** is ***less potent*** and ***shorter-acting***. **Aminophylline** is the ***preferred*** **injectable product** owing to ***increased*** **solubility**.
- ***Mechanism of actions***; **Methylxanthines** have ***several*** **mechanisms**, the ***main*** **mechanisms** are;
  1) ***Inhibits*** **phosphodiesterase enzyme** → ***increase*** **cyclic adenosine monophosphate (cAMP)**;
     - *In* **smooth muscle** → ***relaxation*** **(bronchodilatation)**.
     - *In* **cardiac muscle** → ***contraction*** **(*increase* heart rate)**.
  2) ***Block*** **adenosine receptors**; - *In* **heart** → ***increase*** **heart rate**. - *In* **brain** → **Stimulant effect**.

Methylxanthines have been used for **asthma** for ***more than*** **50 years**, but their use in ***recent years*** has ***declined markedly*** owing to the ***high risk*** of **severe life-threatening toxicity** and **numerous drug interactions**, as well as **decreased efficacy** ***compared with*** **ICSs** and **LABAs** [Narrow Therapeutic Index].

Theophylline (Quibron®)#

- **Theophylline** ***relieves*** **airflow obstruction** in **chronic asthma** and ***decreases*** its **symptoms**.
- ***Dose***; - **Adult**; 300–600 mg/day.
  - **Children**; Start at 10 mg/kg/day.
  - **Pediatric**; Start; 5 mg/kg/day.

Side effects; ***At therapeutic levels***; **Insomnia, GI upset** and **agitation**.
Toxicity; ***At high levels***: **Nausea, vomiting, CNS stimulation, headache, cardiac arrhythmias** and **seizures**.
Drug interactions; **Theophylline** is ***metabolized*** in the **liver** by **CYP1A2** and **CYP3A4**; **Ketoconazole**, **Cimetidine** and **Erythromycin** (***increase*** **Theophylline effect**). **Phenytoin** and **Barbiturates** (***decrease*** **Theophylline therapeutic effect**).

Leukotriene Modifiers (LTMs)

- **Leukotrienes (LTs)** ***result from*** the *action of* **5-lipoxygenase enzyme** ***on*** **arachidonic acid**.
- **LTs** are ***synthesized by*** (*not stored*) a *variety of* **inflammatory cells** in the **airways**, *including* **eosinophils, mast cells, macrophages** and **basophils**.
- **Cysteinyl leukotrienes** (**LTC_4, LTD_4** and **LTE_4**); are a ***potent*** **bronchoconstrictor** (1000 times more potent than histamine), ***increased*** **bronchial reactivity, mucosal edema**, and **mucus** ***hypersecretion***.

Bronchospasm ***occur bout*** **10%** of **people taking NSAIDs**, ***because*** of a ***shift*** in **arachidonic acid** ***from*** **COX** ***to*** **5-LOX**.

Leukotriene Receptor Antagonists (LTRAs); Chronic Asthma

Zafirlukast (Accolate®)# | Montelukast (Singulair®)#

- **Zafirlukast** and **Montelukast** are ***selective*** **antagonists** of the **cysteinyl leukotriene-1 receptor** (**$CysLT_1$ receptor** for **leukotrienes**; **LTC_4, LTD_4** and **LTE_4**).

Zafirlukast and **Montelukast** ***used for*** the ***prophylaxis*** and **chronic** ***treatment*** of **asthma**.
Montelukast ***used in*** **exercise-induced bronchospasm** and ***seasonal*** & ***perennial*** **allergic rhinitis**.
Doses; - **Montelukast**; **once** in the ***evening***;
  - **Adults and children ≥15 years**: 10 mg/day.
  - **Children 6 to <15 years**: 5 mg/day. - **Children 1 to <6 years**: 4 mg/day.

Zafirlukast; **10–20 mg** orally ***twice*** a **day**, **1 hour** ***before*** or **2 hours** ***after*** **meals** (*Bioavailability decreases with food*).

Leukotriene Receptor Antagonists (LTRAs) PRECAUTIONS

- **Neuropsychiatric events**; **behavior** and **mood changes**; **agitation**, **insomnia**, **hallucinations**, **depression**, **irritability**, **restlessness**, **suicidal thinking** and **tremor**.
- **Churg-Strauss syndrome**; is a ***rare*** **systemic vasculitis** *accompanied by* ***worsening*** **asthma**, **pulmonary infiltrates**, and **eosinophilia** in ***people with*** **asthma** who are **steroid-dependent** and who are ***treated with*** **leukotriene receptor** ***antagonists*** **upon reduction** in their ***oral steroid dose***.
- **Hepatotoxicity** ***with*** **Zafirlukast** ***only*** (*monitor symptoms*).
- **Acute asthma attacks**; ***not used*** in **reversal bronchospasm** in **acute asthma attacks** (but continuous used; if acute attack occur during long term control).

\# ***Drug interactions***; **Warfarin**, **Erythromycin** and **Theophylline** ***with*** **Zafirlukast** ***only***; **Zafirlukast** ***inhibits*** **CYP3A4** and **CYP2C9**.

5-lipoxygenase Inhibitors; Chronic Asthma

Zileuton (Zyflo®)#

- **Zileuton** is a ***5-lipoxygenase inhibitor***, ***inhibits*** **leukotrienes formation**.

\# ***Indications***; ***prophylaxis*** & **chronic** ***treatment*** of **asthma** in **adults** & **children ≥ 12 y**.

- ***Dose***; **extended release tablets**; **1200 mg orally** ***twice*** a **day**.

\# ***Warnings and Precautions***; ######## PRECAUTIONS ########

- **Neuropsychiatric events**. - **Churg-Strauss syndrome**.
- **Hepatotoxicity**; **Liver Function Tests**; **LFTs** (***transaminases***); ***should be monitoring***.
- **Acute asthma attacks**.

- ***Drug interactions***; **Warfarin**, **Propranolol** & **Theophylline**; It is ***weak inhibitor*** of **CYP1A2**.

Monoclonal Antibody

Omalizumab (Xolair®)#

\# **Omalizumab** is a ***recombinant*** **anti-IgE** (**human immunoglobulin E**) **antibody** ***approved for*** the **treatment** of **allergic asthma** ***not well controlled*** on **oral corticosteroids** or **ICSs**.

\# ***Mechanism of action***; **Omalizumab** ***decrease*** **binding** of **IgE** to ***its*** **receptor** on the ***surface of*** **mast cells** and **basophils**.

- ***Elimination half-life***; **17** to **22 days**.

\# ***Indications***;

1) **Allergic Asthma**.
2) **Chronic Idiopathic Urticaria (CIU)**.

\# ***Dose***; **150–375 mg SC** ***every*** **2–4 weeks**; **1** or **more** ***injections*** (Do not inject >150 mg per injection site)

\# ***Side effects***; **Injection site reactions** (**urticaria**, **thrombocytopenia**, **malignancy** and **rare anaphylaxis**).

Mast Cell Stabilizers

- **Mast Cell Stabilizers** act by ***stabilize*** the **mast cell** ***membrane***, and ***inhibit*** the **activation** and **release** of **mediators**.
- They ***inhibit*** **acute responses** to **cold air**, **exercise** and **sulfur dioxide**.

Cromolyn Sodium (Intal®) | Nedocromil Sodium (Tilade®)

\# **Cromolyn** and **Nedocromil** are ***mast cell stabilizers***, widely used as ***eye drops*** in **allergic conjunctivitis**.

\# **Cromolyn** (**Intal®**) and **Nedocromil** (**Tilade®**) are an ***inhaled*** ***anti-inflammatory*** **agent** for the ***prophylaxis*** and ***management*** of **asthma**.

- ***Due to*** its ***short*** **duration of action**, this agent ***requires*** dosing **3** or **4 times daily**, which affects adherence and ***limits*** **its use**.
- ***Side effects*** are ***minor*** and *include* **cough**, **irritation**, and **unpleasant taste**.

COPD Managements

1) Smoking Cessation Therapies

Smoking cessation is the ***most important*** **therapeutic intervention** for **COPD**.
Smoking cessation has the ***greatest capacity*** to **influence** the **natural history** of **COPD**.
Long-term **quit smoking** ***success rates*** of ***up to*** **25%** can be ***achieved***.

Nicotine Replacement Therapies

Nicotine (Nicorette®)#

Nicorette® ***products*** (***chewing gum***, ***lozenges***, ***patches***, ***oral spray inhalator***, ***sublingual tablets*** and ***nasal spray***) ***aid in smoking cessation***.
- **Nicotine replacement therapy** ***should be*** **started > 2 weeks** ***after*** a **cardiovascular events** (such as acute coronary syndrome).
- The ***effectiveness*** and ***safety*** of **e-cigarettes** as a **smoking cessation** ***aid*** is ***uncertain at*** **present**.

Varenicline

Varenicline (Chantix®)# (Champix®)#

- **Chantix®** in the USA and **Champix®** in Canada, Europe, Egypt and other countries.
Varenicline is an **oral drug** ***used to*** **quit smoking** ***(treat nicotine addiction)***. ***Act as*** a **partial agonist** in the **nicotinic receptors** (*especially CNS*).
Dose; - **Days 1 to 3** ⇨ 0.5 mg orally once a day.
- **Days 4 to 7** ⇨ 0.5 mg orally twice a day.
- **Days 8 to end of treatment** ⇨ 1 mg orally twice a day.
☞ Patients ***should be*** treated with **Varenicline** for **12 weeks**.
Most common side effects; ☞ **Nausea**, **vomiting**, **headache**, **constipation**, **sleep disturbance** and **unusual dreams**. **Varenicline** are **category C** ***in pregnancy***.

Bupropion

Bupropion (Wellbutrin®)#

Bupropion is a ***weak*** **norepinephrine-dopamine** ***reuptake*** **inhibitor** (**NDRI**), the ***exact*** **mechanism** of action remains **unknown**.
Dose; - ***Initial***; 150 mg orally once daily for 3 days. - ***Maintenance***; 150 mg orally twice a day.
- ***Duration of therapy***; **12 weeks**, up to 6 months.
Most common side effects; ***increased*** **risk of seizures**, **insomnia**, **anxiety**, **irritability**, **headache**, and ***decreased*** **appetite**.
Warning; ***should not be*** **prescribed** to individuals with **epilepsy** (***lower*** the **seizure threshold**).

2) Vaccinations

All patients with **COPD** ***should*** **receive** the **influenza vaccine** ***yearly*** (*see page;* 36) and the **Pneumococcal Conjugate Vaccine** (**PCV**) ***once*** *before* **age 65**; then a **one-time** ***revaccination*** **5 years** or ***more*** *after* the ***first*** **vaccination**; **CDC** ***recommends*** **PCV** for;
* ***All children*** **<2 years old**. * ***All adults*** **≥ 65 years old**.
* **People 2-64 years old** *with* ***certain*** **medical conditions**.

- **Pneumococcal Polysaccharide Vaccine** (**PPSV23**) (**Pneumovax®23**);
  - **PPSV** ***contains*** **23** purified ***capsular*** **polysaccharide antigens** of ***Streptococcus pneumoniae***.
  - **Antibody** ***levels*** **remain** ***elevated*** for ***at least*** **5 years**.
- **Pneumococcal Conjugate Vaccine** (**PCV13**) (**Prevnar-13®**);
  - **PCV** ***contains*** **13** purified ***capsular*** **polysaccharide antigens** of ***S. pneumoniae*** *conjugated to* **carrier protein**.
  - -The 13 **apsular** ***types*** are ***all*** in **PPSV23** ***except*** for **one**.
  - If **both** **PCV13** and **PPSV23** are ***required***, **PCV13** ***should be*** **given** ***first***, *followed by* **PPSV23** ***at least*** **8 weeks** ***later***. If **PPSV23** is ***given*** **first**, **PCV13** ***should be*** **given** ***at least*** **6–12 months** ***later***.
  - **PCV13** is ***routinely*** (**Vaccination Schedule**) **given** to **children** at **2**, **4**, **6**, and **12–15 months** of ***age***.

3) Pharmacologic Therapy

β_2-agonists

Short-acting β_2-adrenoceptor Agonists (SABA); 4-6 hours

Salbutamol or **Albuterol** (Ventolin®)#

Levosalbutamol or **Levalbuterol** (Chronsalbutam®)

Terbutaline (Bricanyl®)# | **Pirbuterol** (Maxair®)#

Long-acting β_2-adrenoceptor Agonists (LABA); 12 hours

Formoterol (Foradil®)# | **Salmeterol** (Serevent®)# | **Arformoterol** (Brovana®)

Ultra-Long-acting β_2-adrenoceptor Agonists (Ultra-LABA); 24 hours

Indacaterol (Onbrez® Breezhaler®)#

Olodaterol (Striverdi® Respimat®)# | **Vilanterol** (Breo® Ellipta®)# (Anoro® Ellipta®)#

Anticholinergics

Short-acting Muscarinic Antagonist (SAMA); <12 hours

Ipratropium (Atrovent®)# | **Oxitropium** (Oxiven®)#

Long-acting Muscarinic Antagonist (LAMA); 12-24 hours

Tiotropium (Spiriva®)# | **Umeclidinium** (Incruse® Ellipta®)#

Aclidinium (Tudorza®)# | **Glycopyrronium** (Seebri® Breezhaler®)#

Methylxanthines

Theophylline (Quibron®)#

Combining Bronchodilators

Product	β_2-agonist	Anticholinergic
# Combivent®	Salbutamol (SABA)	Ipratropium (SAMA)
# Atrovent® Comp	Fenoterol (SABA)	Ipratropium (SAMA)
Duaklir® - Brimica®	Formoterol (LABA)	Aclidinium (LAMA)
Bevespi Aerosphere®	Formoterol (LABA)	Glycopyrronium (LAMA)
Utibron® Neohaler®	Indacaterol (LABA)	Glycopyrronium (LAMA)
Anoro® Ellipta®	Vilanterol (LABA)	Umeclidinium (LAMA)
Stiolto® Respimat®	Olodaterol (LABA)	Tiotropium (LAMA)

Inhaled Corticosteroids (ICSs)

Beclomethasone (Beclosone®) | **Fluticasone** (Flovent®) (Flixotide®)#

Mometasone (Asmanex®)# | **Budesonide** (Pulmicort® Flexhaler)#

Triamcinolone (Azmacort®)# | **Flunisolide** (Aerospan®) | **Ciclesonide** (Alvesco®)#

- **β_2-Agonist/Inhaled Corticosteroid Combinations**;

Product	Corticosteroid	β_2-Agonist
# Symbicort®	Budesonide	Formoterol
Dulera®	Mometasone	Formoterol
Fostair®	Beclomethasone	Formoterol
Advair® - Seretide®	Fluticasone	Salmeterol
Breo® Ellipta®	Fluticasone	Vilanterol

Triple Inhaled Therapy (ICS/LABA/LAMA)

- ***Recommendations***; * ***Triple therapy*** **ICS/LABA/LAMA** ***improve*** **lung function, symptoms** and **health status** and ***reduce*** **exacerbations** ***compared to*** **ICS/LABA** or **LAMA** ***monotherapy***.
- ***Products***;
  - **Triohale**® Pressurized Metered-Dose Inhaler (pMDI); **Ciclesonide/Formoterol/Tiotropium** has been marketed as the ***world's first*** **triple-combination inhaler** to be taken only **once** a **day** and is already available in **India**.
  - **Trelegy**® **Ellipta**®; **Fluticasone Furoate/Umeclidinium/Vilanterol**; **FDA** ***Approved*** **(GSK)**.
  - .....®; **Mometasone/Indacaterol/Glycopyrronium**; ***Preregistration*** by **Novartis**.
  - .....®; **Budesonide/Formoterol/Glycopyrronium**; ***Preregistration***.
  - .....®; **Beclomethasone/Formoterol/Glycopyrronium**; ***Preregistration***.

Oral Glucocorticoids (OCSs)

- ***Recommendations***; * ***Chronic treatment*** with **OCSs** ***should be*** **avoided** because of an ***unfavorable*** **benefit-risk ratio**.
  * **OCSs** used treating ***acute exacerbations*** in **hospitalized patients**, or ***during*** **emergency**.

Phosphodiesterase-4 (PDE_4) inhibitors

Roflumilast (Daxas®)# (Andomilast®) (Dalivent®) (Westabreath®)

Roflumilast is a ***PDE_4 inhibitor***, is an ***anti-inflammatory***, ***not*** **bronchodilator**.
Mechanism; ***Reduces*** **inflammation** through ***inhibition*** of the **breakdown** of **intracellular cAMP**, ***no*** **direct bronchodilator activity**.
Indication: ***reduce*** the ***risk*** of **COPD exacerbations** in ***patients with*** **severe COPD** ***associated with*** **chronic bronchitis** and a **history of exacerbations**.
Dose; **500 mcg orally** ***once daily***.
Side effects; **Diarrhea**, **weight loss** (*monitoring body weight*) or ***decreased*** **appetite**, **nausea**, **headache**, **back pain**, **influenza**, **insomnia** and **dizziness**.
- ***Contraindications***: ***Moderate*** to ***severe*** **liver impairment**.
- ***Drug interactions***: With ***strong*** **CYP450 enzyme** ***inducers*** or ***inhibitors***.

Antibiotics

Azithromycin | Erythromycin

- ***Recommendations***;
  * **Azithromycin** (250 or 500 mg/day three times per week) or **Erythromycin** (500 mg two times per day) for ***one year*** in **patients** ***prone to*** **exacerbations** ***reduced*** the ***risk of*** **exacerbations** *compared to* **usual care**.
  * **Azithromycin** use was ***associated with*** an ***increased*** *incidence of* **bacterial resistance** and ***impaired*** **hearing tests**.

Mucolytic and Antioxidant Agents

- In **COPD patients** ***not receiving*** **inhaled corticosteroids**, ***regular treatment*** with **Mucolytics** such as **Carbocysteine** and **N-acetylcysteine** (**NAC**) may ***reduce*** **exacerbations** and ***improve*** **health status**.
- ***Recommendations***; * ***Regular*** **use** of **NAC** and **Carbocysteine** ***reduce*** the ***risk of*** **exacerbations** in **selected patients**.

Alpha-1 Antitrypsin Augmentation Therapy

Alpha-1 Proteinase Inhibitor (Zemaira®)

- **Patients** ***with*** **α_1-antitrypsin deficiency** **(AATD)** ***usually*** are **white**, usually ***develop*** **COPD** at a **young age** (***younger than*** **45 years**), and have a ***strong*** **family history**.
- **IV** ***augmentation therapy*** has been ***recommended for*** *individuals with* **AATD**.
- ***Recommendations***;* **IV** ***augmentation therapy*** may ***slow down*** the ***progression of*** **emphysema**

Allergic Rhinitis Medications

- **Allergic rhinitis** (**AR**); is an ***inflammatory***, **IgE-*mediated* disease** *characterized by* **nasal congestion**, **rhinorrhea** (nasal drainage), **sneezing** and/or **nasal itching**.
- ***Pharmacological Management***;
  1) ***Intranasal* Corticosteroids** (***strong recommendation***); **1st line**; Moderate-Severe
  2) ***Oral* Antihistamines** (***strong recommendation***); **1st line**; Mild-Moderate
  3) ***Oral* Leukotriene Receptor Antagonists** (***recommendation***); Coexistent asthma
  4) ***Intranasal* Antihistamines** (***option***); If symptoms not improved with oral antihistamines
  5) **Decongestants** (***option***); Short term-use if congestion not improved with INCs
  6) ***Intranasal* Mast-Cell Stabilizer** (***option***); Before exposure to specific known allergy
  7) ***Intranasal* Anticholinergics** (***option***); For sever persistent rhinorrhea
  8) ***Combination* Therapy** (***option***); If inadequate response with monotherapy

1) *Intranasal* Corticosteroids (INCs)

First Generation

Beclomethasone (Becol®)#	**Triamcinolone** (Nasacort® AQ)#
Flunisolide (Nasarel®)#	**Budesonide** (Rhinocort® Aqua)#

Second Generation

Fluticasone Furoate (Avamys®)#	**Fluticasone Propionate** (Flonase®)#
Mometasone (Nasonex®)#	**Ciclesonide** (Omnaris®)
Betamethasone (Betnesol®)	

***First generation* intranasal corticosteroids** are ***more* bioavailable** and tend to *produce* ***more* systemic adverse effects** than ***second generation* intranasal corticosteroids** are ***less* bioavailable** and have ***limited* systemic adverse effects**.

Mechanism; act by ***decreasing*** the ***influx of* inflammatory cells** and ***inhibiting*** the ***release of* cytokines**, thereby ***reducing* inflammation** of the **nasal mucosa**.

Onset of action; ***within* 12 hours**. # ***Maximum Effectiveness***; **2-4 weeks** *of use*.

Pregnancy; ***only* Budesonide** has an **FDA pregnancy** ***category* B** & ***others*** are **C**.

Local side effects; **throat irritation**, **epistaxis**, **stinging**, **burning** and **nasal dryness**.

Systemic side effects; ***No*** or ***limited* effects** on **Hypothalamic-pituitary-adrenal (HPA)** ***axis*** *suppression* and ***decreased* vertical growth** of **children** [***all* intranasal corticosteroids *carry*** a **warning** that ***long-term use*** may ***restrict* growth** in **children**].

2) *Oral* Antihistamines

Second Generation

Cetirizine (Zyrtec®)#	**Loratadine** (Claritin®)#	**Acrivastine** (Semprex®)#
Ebastine (Kestine®)#	**Mizolastine** (Zolim®)#	

Third Generation

Levocetirizine (Allear®)#	**Desloratadine** (Aerius®)#	**Fexofenadine** (Telfast®)#

Second and ***third*-generation* antihistamines** have a ***better* adverse effect *profile*** and *cause* ***less* sedation**, with the ***exception of* Cetirizine** (**Zyrtec®**) [***partially* sedating**].

Onset of action; **15** *to* **30** ***minutes***.

Oral Antihistamines; ***safe*** for **children ≥ 2 years**.

Pregnancy; **Cetirizine** and **Loratadine** are **FDA pregnancy** ***category* B**, while **Desloratadine** and **Fexofenadine** are ***category* C**.

3) *Oral* Leukotriene Receptor Antagonists

Montelukast (Singulair®)#

Montelukast; can be ***used*** in ***children*** < 2 years for **allergic rhinitis** and may be ***most beneficial*** in patients who also have **asthma**.
- ***Pregnancy***; **Montelukast** has an **FDA pregnancy** ***category*** **B**.

4) *Intranasal* Antihistamines

Azelastine (Astelin®)#

Intranasal **antihistamines** are an ***option*** for **patients** ***with*** ***seasonal***, ***perennial*** and ***episodic*** **allergic rhinitis**.
Benefits; is **targeted delivery** and ***increased*** **dosage** to **nasal tissues**.
Efficacy; ***similar*** or ***superior*** to **oral antihistamines** for **nasal** ***symptoms*** & *may* ***improve*** **congestion**.
- **Children**; may ***use*** for **children** ≥ 5 **years**.
- ***Pregnancy***; **Azelastine** has an **FDA pregnancy** ***category*** **C**.
Recommendations; **Intranasal antihistamines** are an ***option*** if **symptoms** ***do not*** **improve** *with* **oral** ***second/third-generation*** **antihistamines**; ***because***; **Azelastine** ***twice*** **daily dosing**, ***more expensive***, and ***decreased*** **effectiveness** ***compared with*** **intranasal corticosteroids**.
Local side effects; **bitter taste**, **epistaxis**, **headache**, **somnolence** and **nasal** ***burning***.

5) Decongestants (*Oral/Topical*)

Pseudoephedrine	Phenylephrine
Oxymetazoline (Afrin®)#	**Xylometazoline** (Otrivin®)#

- **Oral** and **intranasal decongestants** ***improve*** **nasal congestion** ***associated with*** **allergic rhinitis** by ***acting on*** α_1-**adrenergic receptors**, which causes ***vasoconstriction*** in the **nasal mucosa**.
- ***Most common*** **decongestants** are **Pseudoephedrine**, **Phenylephrine** & **Oxymetazoline**
- ***Common side effects*** of **intranasal decongestants**; **sneezing** and **nasal dryness**.
Duration of therapy; ***not more*** ***than*** **3-5 days**; ***because*** may ***develop*** **Rhinitis Medicamentosa (RM)**, or **rebound rhinitis** or **recurring congestion**.
Patient Counselling; **Patients** ***using*** **topical decongestants** ***should understand*** that if the **agents** are **used** ***longer than*** **3 days**; ***rebound*** **congestion** [**Rhinitis Medicamentosa (RM)**] *will* **develop**.
Oral decongestants; *may cause* **headache**, ***elevated*** **blood pressure** and **intraocular pressure**, **tremor**, **urinary retention**, **dizziness**, **tachycardia** and **insomnia**.
Pseudoephedrine ***should be*** **used** ***cautiously*** in **patients** ***with*** **cardiovascular disease**, **hypertension**, **diabetes**, **hyperthyroidism**, **closed-angle glaucoma** or **bladder neck obstruction**.
Recommendations; **Decongestants** may be ***considered for*** **short-term use** in ***patients without*** **improvement** in **congestion** with **intranasal corticosteroids**.

6) *Intranasal* Mast-Cell Stabilizer

Cromolyn (Nasalcrom®)#

- **Cromolyn**; **safe** for **children** ≥ 2 **years**. - ***Pregnancy***; **FDA pregnancy** ***category*** **B**.

7) *Intranasal* Anticholinergics

Ipratropium (Atrovent®)#

- **Ipratropium** has ***anti-secretory properties***, and when ***applied*** **locally**, ***inhibits*** **secretions** from **glands** *lining* the **nasal mucosa**.
- **Ipratropium** ***may cause*** **dry nose** and **mouth**, **pharyngeal irritation**.

8) Combination Therapy

- ***Combination*** **therapy** is an ***option*** for **patients** ***with*** ***severe*** or ***persistent*** **allergic rhinitis** who have ***inadequate*** **response** to **monotherapy**.

Cough Medications

Cough; is a ***defense mechanism*** that ***clear*** the **respiratory tract** *from* **mucus** and **irritants** such as **dust** or **smoke**.
- **Coughing** is either ***voluntary*** or ***involuntary***.
Cough reflex is ***stimulated from*** **afferent cough receptors** *located in* the **upper** and **lower respiratory tract, pericardium, oesophagus, diaphragm** and **stomach**.
- **BEFORE treating cough**; ***identification*** of its **cause** is **important** to ***ensure*** that **antitussive treatment** is ***appropriate***.
Cough Classifications;
  * ***According to*** **durations**;
    - **Acute** (***sudden onset***); if it is present ***less than*** **3 weeks**.
    - **Subacute**; if it is present ***between*** **3** and **8 weeks**.
    - **Chronic**; when **lasting** ***longer than*** **8 weeks**.
  * ***According to*** **character**;
    - **Dry**; ***non-productive*** (***no*** **phlegm** or **mucus** or **sputum** is **produced**).
    - **Productive** or **wet**; **coughs** that ***produce*** **phlegm** or **mucus** or **sputum**.
The **FDA** ***does not*** **recommend OTC cough** and **cold drugs** (containing nasal decongestants, antihistamines, cough suppressants and expectorants) for use in **children** ***younger than*** **6 years** for ***treatment of*** **URTI symptoms**.
For children, the ***only*** **products** that can be **beneficial** *are* **Honey** (older than 1 year) and **VaporRub®** (older than 2 year).

Antitussives or Cough Suppressants

Cough suppressants ***must not be used*** to ***treat*** **productive cough**, which is ***considered to*** be a **useful protective mechanism**.

Central Antitussives

- ***Mechanism of action***; 1) ***Depression*** of **medullary cough center**.
  2) ***Increased*** **threshold** of **cough center**.

Opioid/Narcotic/Addicting Antitussives

Potent Addictive Opioids

Morphine

Less Addictive Opioids

Codeine

Non-Addictive Opioids

Dextromethorphan

Dextromethorphan is ***free*** of **addictive properties** and produces ***less*** **constipation** than **Codeine**.
It is ***one*** of the **active ingredients** in ***many*** **OTC cough medications**.
The ***primary use*** of **Dextromethorphan** is as a **cough suppressant** (***antitussive***).
Dextromethorphan is the ***most commonly*** **used** ***agent*** as **antitussive**.
Dose; **15-30 mg** ***every*** **6-8 hr**. - ***Pregnancy category***; **FDA**; **C** and **AU TGA**; **A**.
At ***high*** **doses** **Dextromethorphan** acts as an **NMDA** ***antagonist*** (**Hallucinations**).
Dextromethorphan & **Codeine** are ***available*** in ***combination with*** **Guaifenesin**!?
- It is ***should not*** be taken with **MAOIs** due to the ***potential for*** **serotonin syndrome**.

Noscapine

- **Noscapine** is a ***non-narcotic*** **alkaloid** *derived from* **opioids**, with ***mild*** **analgesic**, **antitussive**, and ***potential*** **antineoplastic** ***activities***.
- **Noscapine**, and its ***synthetic derivatives*** called **Noscapinoids** (***new class*** of **anticancer drugs**) are known to ***interact with*** **microtubules** and ***inhibit*** **cancer cell** ***proliferation***.
- ***Dose***; **15-30 mg orally 3-4 times daily**. # # # ***Pregnancy*** ***category***; **X**.

Non-opioids/Non-narcotic/Non-addicting Antitussives

Diphenhydramine | Promethazine | Chlorpheniramine

First generation **antihistamines** (**cross BBB**; central mechanism) are ***now*** *can* ***used as*** **antitussives**.

Mechanism; They ***relieve*** **cough** *due to their* **sedative** (***central***) and **anticholinergic actions**, *but* **lack** ***selectivity*** for **cough center**.

Many **antihistamines** have been ***added to*** **antitussive/expectorant** ***formulations***.

Butamirate (Sinecod®)#

Butamirate is a ***central non-narcotic*** **antitussive**.

- ***Mechanism***; ***depress*** **cough center** *with* ***moderate*** **bronchodilator** ***effect***.

Butamirate ***can be used*** *even* in **infants** (**Sinecod®** *drops*).

Butamirate **produce** ***efficacy*** *similar to* **Dextromethorphan** with ***safe profile***.

- ***Dose***; **7.5 mg/5mL**; - ***Adult*** **15 mL 4 times daily** - ***Child***; **5 mL 3 times daily**.

Cloperastine (Notussil®) | Dropropizine (Tussapine®)#

Clobutinol (Silomat®)#

Clobutinol has the ***potential*** to ***prolong*** the **QT interval**, it was **voluntarily** ***withdrawn*** from ***some*** **countries** (**Germany**).

Oxeladin (Paxeladine®)#

Oxeladin is a ***highly potent*** and ***effective*** **antitussive** **drug** used to treat ***all types*** of **cough** *because* it ***helps to*** *clear* the **respiratory tract** *from* ***excess*** **secretions**.

Pentoxyverine (Solotuss®) (Cabella®)#

Pipazethate or Pipazetate (Selgon®)#

Pipazethate is a ***central and peripheral*** **antitussive** by ***inhibition of*** **cough center** and **peripheral neural** ***receptors*** in the **lung**. It has a ***bronchodilator effect*** which ***reduce spasm*** *during* **cough**.

- It may be ***used*** at **every age** (*available as* **drops**, **tablets** and **supp.**).
- ***Adult dose***; **20 mg orally** ***3 times daily***.
- ***Pregnancy*** ***category***; **N** (FDA has not classified the drug).

Benproperine (Pectipro®)#

Peripheral Antitussives

Peripheral Cough Reflex Inhibitors

Benzonatate (Tessalon®)

- **Benzonatate** ***suppresses*** the **cough reflex** through ***peripheral*** **action**.

Benzonatate is **chemically** ***related to*** the **ester-linked class** of **local anesthetic drugs**.

- It ***works by*** **anesthetizes** ***peripheral*** **neural receptors** (**stretch receptors**) in the **lung**.
- ***Adult dose***; **100-200 mg orally** ***3 times daily***.
- ***Pregnancy*** ***category***; **C**.
- *Excessive* **absorption** of **Benzonatate** in the **oral mucosa** will result in the ***rapid development*** of **numbness** of the **mouth** and **throat**.

Others

Honey; ***effective*** *for* ***relieving*** **cough**, and ***improving*** **sleep** in **children**. ***Dose***; **8.5 mg** (**½ tsp**) for ***ages*** **2-5 years**, **17 mg** (**1 tsp**) for ***ages*** **6-11 years**, and **34 mg** (**2 tsp**) for ***ages*** **12-18 years**, *administered as* a **single dose 30 minutes** ***before*** **bedtime**; ***Should not*** be used in **children < 1 year** *because* of possible ***contamination with*** *Clostridium botulinum*.

Chest rub; **Vicks® VaporRub®** ; is a ***topical*** **petrolatum-based gel** ***contains*** **Menthol**, **Eucalyptus oil** and **Camphor**, ***applied*** **once** to the **upper chest** and **neck** ***before*** **sleep** at a dose of **5 mL** for **children** ***ages*** **2-5 years** and **10 mL** for **children** ***ages*** **6-11 years**.

NSAIDs; **Naproxen**; The ***only*** **NSAID** ***recommended*** in the **guidelines** for treatment of **cough** ***associated with*** **common cold** (because it was the only NSAID studied in this setting).

Inhaled **Ipratropium**; ***recommended in*** ***post-infectious*** **cough** or **chronic bronchitis**.

ICS; ***recommended in*** ***post-infectious*** **cough** if ***Inhaled*** **Ipratropium** is ***not effective***.

- **N.B.**; ***Central-acting*** **antitussives**; are ***recommended in*** ***post-infectious*** **cough** if ***both*** ***Inhaled*** **Ipratropium** and **Inhaled Corticosteroids** (**ICS**) are ***ineffective***.

Mucolytics/Mucoregulators/Mucokinetics

N-AcetylCysteine (NAC)

N-Acetylcysteine (**NAC**) is a **mucolytic** and **antidote** (**Paracetamol** toxicity) **drug**, with ***antioxidant*** and ***anti-inflammatory properties***.

- ***Mechanism of action***;
  - ***Decreases*** **thickness** (**viscosity**) of **mucous secretions** in **lung**; by ***breaks*** **disulphide bonds** in ***mucoprotein*** (**mucin**) in **sputum**.
  - ***Protects*** **liver** by ***maintaining*** or ***restoring*** **glutathione** ***levels***.

Uses; - ***Adjuvant therapy*** for ***patients with*** **abnormal mucous secretions**; *such as* **emphysema**, **cystic fibrosis** and **chronic obstructive pulmonary disease** (**COPD**).
  - ***Prevention*** or ***decreasing*** of **liver damage** after **Paracetamol toxicity**.

Dose; in ***abnormal*** **mucous** ***secretions***;
  - ***Inhalation***; 1-2 mL of 10% solution may be given as often as every hour.
  - ***Direct instillation*** (into respiratory tract); 2-5 mL of the 20% solution.
  - ***Nebulization***; 3-5 mL of 20% solution or 6-10 mL of the 10% solution 3 to 4 times a day; DON'T mix with antibiotics in the same nebulizer.

Pregnancy ***category***; **B**.

#There are ***several*** **similar compounds** that **contain sulfhydryl groups** *such as*, **MethylCysteine** and **N-Acystelyn** (**lysine salt** *alternative to* **NAC**) that can ***effectively depolymerize*** **mucin polymers**.

Erdosteine (Mucotec®)#

Erdosteine is a **mucolytic** ***agent*** with ***antioxidant properties***.

Erdosteine is ***prodrug*** *contains* ***2*** blocked **sulfhydryl** (**SH**) **groups** which are ***released*** ***following*** **first-pass metabolism**. The **3 active metabolites** ***exhibit*** **mucolytic** and ***antioxidant*** **activity**.

- ***Dose***; **150-300 mg orally twice** ***daily***.

Bromhexine (Bisolvon®)#

Bromhexine is a **mucolytic expectorant** ***agent*** with ***antioxidant properties***.
- ***Dose***; **4-8 mg orally 3-4** ***times daily***. # ***Pregnancy category***; **A**.

CarboCysteine or Carbocisteine or CarboxyMethylCysteine (Mucosol®)#

CarboCysteine (**Carbocisteine** or **CarboxyMethylCysteine**) is the ***most frequently*** **prescribed mucoactive agent** (**mucoregulator**) for ***long-term*** **COPD** ***use***.
CarboCysteine has ***antioxidant*** and ***anti-inflammatory properties***.
Carbocisteine is ***available as*** an ***oral formulation*** and *achieves* ***good*** **penetration** into **lung tissue** and **bronchial secretions**.
- ***Mechanism of action***; ***Not act*** **directly** *upon the* **mucus structure**, in ***contrast to*** **NAC**.
  - ***Increase*** the **synthesis** of **sialomucins** (important structural components of mucus) → ***restoring*** the **viscoelastic properties** of **mucus**.
  - ***Increase*** **chloride** ***transport*** *across the* **airway epithelium**, which may *contribute towards* its **mucoregulatory** ***action***.
- ***Dose***; **20 mg/kg orally** ***daily*** in *divided doses*. - ***Pregnancy category***; **C**.

Ambroxol (Mucosolvan®)#

Ambroxol is a **secretolytic** (**mucolytic**) and **secretomotoric drug** that ***restore*** the **physiological clearance** ***mechanisms*** of the **respiratory tract**.
Ambroxol is a ***metabolite of*** **Bromhexine**.
- ***Dose***; - ***Adult***: **60-120 mg** ***daily*** in **2-3** ***divided doses***.
  - ***Child***: **2-5 years**: **7.5 mg 3 times** ***daily***. - **6-12 years**: **15 mg** ***twice*** or **3 times** ***daily***.
Pregnancy; ***avoid use*** *during* the **first trimester** of **pregnancy**.

Expectorants

- **Expectorants**; **Drugs** that ***expulsion*** of **mucus** ***from*** the **respiratory tract**. This ***typically*** **requires** a **coughing** ***action*** to ***loosen*** and **bring up** the **mucus** *from* the **respiratory tract**.
  - **Guaifenesin** (**glyceryl Guaiacolate**) is an ***expectorant drug*** **sold OTC**.
  - **Syrup of ipecac** (***Ipecacuanha***); is a ***powerful*** **emetic**, used in ***cough mixtures*** as an **expectorant** or an **emetic** from the 18th until the early 20th century.
  - **Hypertonic saline**; ***Aerosol inhalation*** of **Saline** or **Mannitol** has been ***previously*** *thought to* ***induce*** **ciliary motility**, **proteolysis** and **mucus liquefaction** by **osmosis**.
  - ***Aerosol inhalation*** of **Ammonium chloride/bicarbonate**, **Sodium/Potassium citrate** and **Potassium iodide**; ***promote*** the **secretion** of **airway fluids**. **Potassium iodide** ***should not*** be *administered to* **pregnant** or **hyperthyroid**.

Guaifenesin or Guaiphenesin or Glyceryl Guaiacolate

Guaifenesin [gwye-FEN-e-sin] is an **expectorant drug** ***sold*** **OTC**.
Guaifenesin has ***no*** **mucolytic** ***action*** but may ***reduce*** **bronchial sputum surface tension** and is *sometimes* ***combined with*** **antitussives**.
- ***Mechanism of action***;
  - ***Increasing*** **volume** and ***reducing*** **viscosity** of **bronchial secretions**.
  - ***Increasing*** **ciliary** ***movement*** and ***increase*** the **efficiency** of the **cough reflex** → ***facilitate*** **removal** of **secretions**.
Guaifenesin has **muscle relaxant** and **anticonvulsant** ***properties*** ***increases*** the **analgesic effect** of **Paracetamol** and **Aspirin**, *increases* **sedative effects** of **alcohol**, **tranquilizers** and **anesthetics**.
- ***Adult dose***; - *Immediate release*; **200-400 mg orally** ***every*** **4 hours**.
  - *Sustained release*; **600-1200 mg orally** ***every*** **12 hours**.
Pregnancy category; **C**.
Guaifenesin (**expectorant**) + **Oxomemazine** (***sedative*** **antihistamine**); **Toplexil®**.

Common Respiratory Tract Infections (RTIs)

- **Respiratory Tract Infections** (**RTIs**) ***further*** **classified as** an;
  - **A) Upper Respiratory Tract Infections** (**URTIs**); **Tonsillitis**, **Pharyngitis**, **Laryngitis**, **Sinusitis**, **Otitis Media** and **Common Cold**.
  - **B) Lower Respiratory Tract Infections** (**LRTIs**); **Bronchitis** and **Pneumonia**;

Influenza

- It can be ***difficult*** to ***distinguish*** *between* the **common cold** and **influenza** in the ***early*** **stages** of *these* **infections**;

Signs and Symptoms	Influenza (Flu)	Common Cold (Cold)
Onset	Sudden	Gradual
Temperature	High (>38°C) of 3–4 days duration	Occasional
Cough	Dry (can become severe)	Hacking*
Headache	Prominent	Occasional
Myalgia (muscle aches & pains)	Usual; often severe	Slight
Tiredness and weakness	Can last 2–3 weeks	Very mild
Extreme exhaustion	Early and prominent	Never
Chest discomfort	Common	Mild to moderate
Stuffy nose	Sometimes	Common
Sneezing	Sometimes	Usual
Sore throat	Sometimes	Common

* Hacking cough; a small and frequent cough, usually short and dry; a broken cough with a rough and loud sound.

- **Pharmacotherapy** (***Recommendations***);
  - ***Early*** **antiviral treatment** can ***reduce*** the ***risk of*** **complications** from **influenza** (e.g., **pneumonia**, **respiratory failure**, and **death**);
    - ***Should be*** **started** ***as soon as*** **possible** *after* **illness** ***onset***.
    - ***Greatest*** **benefit** is when **antiviral treatment** is ***started*** *within* **48 hours** of **influenza illness** ***onset***.
  - ***Recommended*** **antiviral medications**; **ONLY** **Neuraminidase Inhibitors** (**NAIs**); **Oseltamivir** OR **Zanamivir**; **Initiate** ***within*** **48 hours** of **symptom** ***onset***.
    - ***Doses***;
      - **Oseltamivir** (**Tamiflu®**); ***Duration of therapy***: **5 days**;
        - <15 kg: 30 mg *orally* twice daily.
        - 15-23 kg: 45 mg *orally* twice daily.
        - 23-40 kg: 60 mg *orally* twice daily.
        - >40: 75 mg *orally* twice daily.
      - **Zanamivir** (**Relenza®**); **10 mg** (**2** ***inhalation tab.***) **twice** for **5 days**.
    - ***Side effects***;
      - **Oseltamivir**; **GI discomfort** and **nausea** (**taking** *with* **food**).
      - **Zanamivir**; **Headache**, **throat/tonsil pain** and **cough**.
  - **Pre-exposure Chemoprophylaxis**; For **4-6 weeks** ***during*** peak **influenza season**.
  - **Post-exposure Chemoprophylaxis**; **No** ***more than*** **10 days**.
    - **Oseltamivir** (**Tamiflu®**) and **Zanamivir** (**Relenza®**); Dosages for **chemoprophylaxis** are the ***same*** for **treatments**, but doses are administered **ONLY once** per day ***rather than*** **twice**.
- **Prevention**; **Immunizations Related to** the **Respiratory Tract**;
  - **A) Pneumococcal vaccines**; see page no 95.
  - **B) Seasonal Flu Vaccine** (**Flu Shots**); see page no 46.

Sinusitis (Sinus Infection or Rhinosinusitis)

- **Sinusitis** is ***inflammation*** of the **mucosal** ***lining*** of the **nasal passage** & **paranasal sinuses** ***lasting up*** to **4 weeks**.
- **Causes**; *including* **viruses** (more than 90%), **bacteria** (less than 10%) and **fungi**.
- ***Streptococcus pneumoniae*** and ***Haemophilus influenzae*** are ***common*** **bacterial pathogens**.
- ***Common*** **signs** and **symptoms** include ***thick*** **nasal mucus**, a ***plugged*** **nose**, and **pain** in **face**.
- **Acute sinusitis** (***last up to*** **4 weeks**); ***usually*** **viral** (common cold or influenza); ***lasts up to*** **10 days** and that ***completely*** **resolves** in **99%** *of* **cases**.
- **Chronic sinusitis** (***last up to*** **12 weeks**); **bacterial infection**.
- **Subacute sinusitis** (***lasts*** *between* **4 & 12 weeks**); a ***transition*** *between* **acute** and **chronic infection**.
- **Diagnosis**; ***Presence*** of at ***least*** **2 major** ***symptoms*** OR
  1 major and **2** or **more minor symptoms**;

Major Symptoms	Minor Symptoms
Purulent anterior nasal discharge	Headache
Purulent or discolored posterior nasal discharge	Ear pain, pressure, or fullness
Nasal congestion or obstruction	Halitosis (Bad breath)
Facial congestion or fullness	Dental pain
Facial pain or pressure	Cough
Hyposmia or anosmia	Fever (for subacute or chronic sinusitis)
Fever (for acute sinusitis only)	Fatigue

- **Differentiating Viral** ***from*** **Bacterial Sinusitis**;

	Viral	Bacterial
Symptoms	Nasal discharge, congestion and scratchy throat.	
Nasal discharge	Clear *to* purulent *to* clear; Purulence not present until days 4–5	Persistent purulent discharge (>10 days) or early and severe (first 3–4 days) or increased on days 5–6 after typical viral infection (double-sickening)
Fever	None (or early in course, resolving in 48 hours)	High temperature (≥39°C) and early (first 3–4 days)
Other symptoms	Headache, facial pain, and myalgia (resolving in 48 hours)	Headache, facial pain, myalgia, daytime cough
Peak symptoms	Days 3–6	Persistent >10 days or early and severe (first 3–4 days) or improved symptoms that worsen on days 5–6
Duration	5–10 days	In general; >10 days

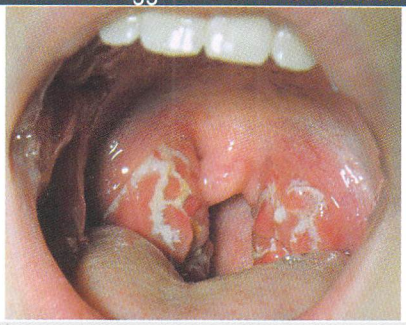
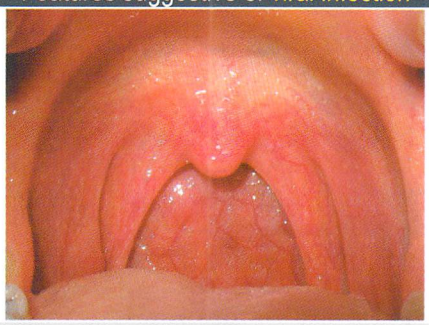
- **Pharmacotherapy** (***Recommendations***); **Acute Bacterial Sinusitis**
  - ***First-line*** **therapy**; **Amoxicillin/Clavulanate** (**Augmentin®**).
    - ***High-dose*** **Amoxicillin/Clavulanate**;
      - **2 g** ***twice*** **daily** in **adults** (**Augmentin® XR**) OR
      - **90 mg/kg/day** *divided* ***twice*** **daily** (**Augmentin® ES-600**) in ***high*** **risk patients**.
  - ***Second-line*** **therapy**;
    - **Respiratory fluoroquinolone** (*including* **children** with **type I hypersensitivity to Penicillin**).
    - **Doxycycline**
    - **Cefixime** OR **Cefpodoxime** *with* **Clindamycin** (for ***children*** with **non–type I hypersensitivity to Penicillin**).
    - ***Intranasal*** **saline irrigation** as adjunctive therapy.
    - ***Intranasal*** **corticosteroids** as adjunctive therapy in ***patients with*** **allergic rhinitis**.
  - ***Duration of therapy***; ***Adults***: **5–7 days** - ***Children***: **10–14 days**.

Acute Pharyngitis

- **Pharyngitis** is ***inflammation*** of the **back** of the **throat** (**pharynx** or **tonsils**). It **typically** *results* in a **sore throat** and **fever**.
- **Causes**; *usually* **infectious**, with ***most cases*** being of **viral *origin*** and ***most* bacterial *cases*** *attributable to* ***Streptococcus pyogenes*** (**Group A *Streptococcus*** [**GAS**] OR **Group A *β*-hemolytic Streptococci** [**GABHS**]). Other causes include allergy, trauma, toxins, and neoplasia (***bacterial* causes**, *known as* **strep throat**).
- **Seasonal outbreaks *occur***, and the ***incidence*** of **GAS** is ***highest*** in **winter** and ***early* spring**.

Acute rheumatic fever is rarely seen in developed countries. In the United States, acute rheumatic fever secondary to GAS infection was a cause of concern in the 1950s and was the major reason for penicillin therapy, but the annual incidence of this disease today is extremely rare (≤1 case per 1 million population). However, some risk does remain.

* **GAS *VS* Viral Pharyngitis**;

Features suggestive of GAS infection	Features suggestive of viral infection
	
Beefy, swollen, red uvula	Characteristic enanthems (rash on mucous membranes)
Fever	Characteristic exanthems (widespread rash)
Headache	Conjunctivitis
History of exposure to GAS	Coryza (Rhinitis)
Nausea, vomiting, and abdominal pain	Cough
Pain with swallowing	Diarrhea
Patient 5 to 15 years of age	Hoarseness
Presentation in winter or early spring (in temperate climates)	- Causes; - Rhinovirus; 20% of cases of pharyngitis. - Adenovirus; most commonly caused by adenovirus types 1-3 & 5 - **Epstein-Barr Virus** (**EBV**) (**Mononucleosis** or **kissing Disease**); usually spreads from adults to infants. Among young adults, EBV spreads through saliva and, rarely, through blood transfusion. Pharyngitis or tonsillitis is present in about 82% of patients with infectious mononucleosis. - Other Viruses; Herpes simplex virus, Influenza virus and Coronavirus.
Scarlet fever rash	
Soft palate petechiae (doughnut lesions)	
Sudden onset of sore throat	
Tender, enlarged anterior cervical nodes	
Tonsillopharyngeal erythema	
Tonsillopharyngeal exudates	

If clinical and epidemiologic findings suggest GAS infection, microbiologic confirmation with a throat culture or rapid antigen detection test (RADT) is required.

- **Pharmacotherapy** (***Recommendations***); **Acute Bacterial Pharyngitis**
  - * ***Primary* prevention** of **rheumatic fever** *requires* ***adequate* therapy** for **GAS pharyngitis**.
  - * ***Early* initiation** of **antibiotic therapy** ***results in* faster resolution** of **signs** and **symptoms**.
  - * ***Delays*** in **therapy** (if ***awaiting* cultures**) can be *made* ***safely*** *for up to* **9 days *after* symptom onset** and *still* ***prevent major* complications** *such as* **rheumatic fever**.
  - * **Patients** are ***no longer* considered *contagious*** *after* **24 hours** of **antibiotic therapy**.
  - * *For over* **30 years**, **GAS *isolated*** in the **United States** has shown ***susceptibility*** to **Penicillin**.

* Treatment;
  * Pain Management (Paracetamol, NSAIDs, Lozenges or Sprays containing menthol and topical anesthetics); for temporary relief of pain.
  * Antibiotic therapy (Primary Prevention of Rheumatic Fever);

Preferred Antibiotics			
	Adult Dosage	Pediatric Dosage	Duration
Amoxicillin	500 mg 3 times daily	40–50 mg/kg/day divided in 3 doses	10 days
Penicillin V	250 mg 3 or 4 times daily or 500 mg twice daily	50 mg/kg/day divided in 3 doses	10 days
Benzathine Penicillin	>27 kg; 1.2 million units IM	≤27 kg; 0.6 million units IM	Once
Additional Effective Antibiotics (*for patients allergic to penicillin*)			
Cephalexin	250–500 mg 4 times daily	25-50 mg/kg/day divided in 4 doses	10 days
Azithromycin	12 mg/kg once daily (maximum 500 mg)		5 days
Clarithromycin	15 mg/kg per day divided in 2 doses (maximum 250 mg twice daily)		10 days
Clindamycin	20 mg/kg per day divided into 3 doses (maximum 1.8 g/day)		10 days

  * Secondary Prevention of Rheumatic Fever;
    - Duration of therapy;

Rheumatic fever with carditis and persistent valvular disease	10 years or until age 40 years (whichever is longer)
Rheumatic fever with carditis but no valvular disease	10 years or until age 21 years (whichever is longer)
Rheumatic fever without carditis	5 years or until age 21 years (whichever is longer)

    - Antibiotic Therapy;

	Adult Dosage	Child Dosage
Preferred Antibiotics		
Benzathine Penicillin	>27 kg; 1.2 million U IM every 4 weeks	≤27 kg; 0.6 million U IM every 4 weeks
Penicillin V	250 mg orally twice daily	
For individuals allergic to Penicillin		
Sulfadiazine	1000 mg every 24 hours	500 mg every 24 hours
For individuals allergic to Sulfonamide or Penicillin		
Azithromycin	6 mg/kg every 24 hours	250 mg every 24 hours
Erythromycin	250 mg every 12 hours	

- Tonsillectomy may be ***considered*** for r ***recurrent*** **throat infection** with a ***frequency*** of ***at least*** **7 episodes** in the ***past*** **year** OR ***at least*** **5 episodes** ***per*** **year** for **2 years** OR ***at least*** **3 episodes** ***per*** **year** for **3 years** with ***documentation*** in the **medical record** for ***each*** **episode** of **sore throat** and **1** or ***more*** of the following: **temperature > 38.3°C**, **cervical adenopathy**, **tonsillar exudate**, or ***positive*** **test** *for* **GAS**.

Acute Otitis Media (AOM)

- Otitis media (OM) is ***any*** **inflammation** of **middle ear**.
- Causes; - **40-75%** of **Acute Otitis Media** are *caused by* **viral pathogens**.
  - ***Common*** **bacterial pathogens**; ***Streptococcus pneumoniae*** (25–50%), ***Haemophilus influenzae*** (15–30%), and ***Moraxella catarrhalis*** (3–20%).
- Pharmacotherapy (***Recommendations***); **Acute Otitis Media**
  * Pain Management (Paracetamol or NSAIDs); ***especially*** *during* the ***first*** **24 hours** of an ***episode*** of **AOM**, ***should be*** *addressed* ***regardless*** of the *use of* **antibacterial agents**.
  * Antibiotic therapy;

	Initial Diagnosis		Failure at 48–72 Hours	
	Non-severe	Severe	Non-severe	Severe
First line	Amoxicillin; ***high-dose***; 80–90 mg/kg/day divided twice daily	Amoxicillin-Clavulanate; ***high-dose***; 90 mg/kg/day divided twice daily	Amoxicillin-Clavulanate; ***high-dose***; 90 mg/kg/day divided twice daily	Ceftriaxone (1–3 days)
Non–type 1 allergy	Cefdinir, Cefuroxime, Cefpodoxime	Ceftriaxone (1–3 days)	Ceftriaxone (1–3 days)	Clindamycin
Type 1 allergy	Azithromycin, Clarithromycin	Clindamycin	Clindamycin	Clindamycin

Common Respiratory Cases

Allergic Rhinitis in Adult

* **Avoid Triggers**; **Pollen, dust mite debris** and **animal dander**.
* *Check for* **acute sinusitis**; if **Purulent discharge** ***present*** >> **Augmentin® 1 gm every 12 hours**
* **First line**; **INCs**; **Avamys®** (**Fluticasone Furoate**) *Nasal Spray*;
  - **2 sprays** in *each* nostril **once daily**.
* **First line**; 2nd/3rd **Antihistamines**; **Telfast®** (**Fexofenadine**) 180 mg tablets;
  - **1 tablet once** ***daily*** at ***evening*** *before* **bed**.
* *If* **Coexistent asthma**; **Singulair®** (**Montelukast**) 10 mg tab; **1 tablet once** ***daily*** at ***evening***.
* **Decongestants**; **Otrivin®** or **Deltarhino®**; **3 times** ***daily*** **NOT exceed than 7 days**.
* **Sea water**; **Physiomer®** or **Alka-Misr®**; **twice** ***daily before*** **decongestant**.
  - **Physiomer® Baby**; (**Unidose** or **Mist**) 100% Seawater Formula used from birth.
  - **Physiomer® Normal Jet**; 100% Seawater used in adults and children over 6 years.
  - **Physiomer® Strong Jet**; 100% Seawater used in adults and children over 10 years.
  - **Physiomer® Hypertonic**; Seawater + Salt; used in adults and children over 2 years.
  - **Physiomer® Eucalyptus**; Seawater + Eucalyptus; adults and children over 6 years.

Rhinitis Medicamentosa (RM)

1) ***Continue*** **Decongestant** (**Otrivin®** or others).
2) ***Start*** with ***second*** **generation INCs**.
   - **Avamys®** (**Fluticasone Furoate**) *Nasal Spray*; **2 sprays** in *each* nostril **once daily**.
3) ***Stop*** **Decongestant** (**Otrivin®** or others) ***after*** **one week** of ***using*** **INCs**.
4) ***Continue*** to **INCs** for **4-6 weeks** (regeneration of new blood vessels and mucosal membrane).

Dry Cough

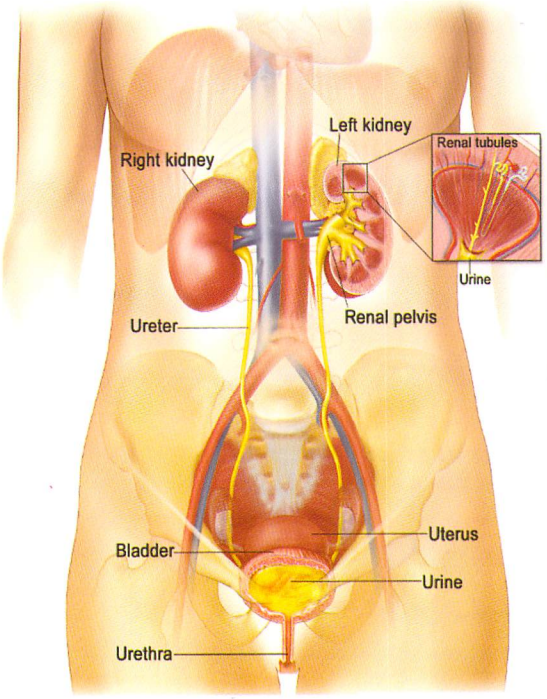
- *Check for*;
  - **Antihypertensive Drugs**; **ACEIs** or **ARBs**.
  - **Gastroesophageal Reflux Disease** (**GERD**).
  - **Asthma Attacks**.
  - **Viral Infection** or **Whooping cough**.
- **Antitussives**; - **Tussivan®N** (**Chlorpheniramine**, **Dextromethorphan**, **Ephedrine** & **Phenylephrine**)
  - **Sinecod®** (**Butamirate**) - **Selgon®** (**Pipazethate**) - **Notussil®** (**Cloperastine**).
- **Herbal Products**; **Bronchicum®** (**Thyme** and **Primula**) - **Balsam®** - **Guaflex®**
- **Home Remedies**; Honey, fluid intake, volatile hot drinks.

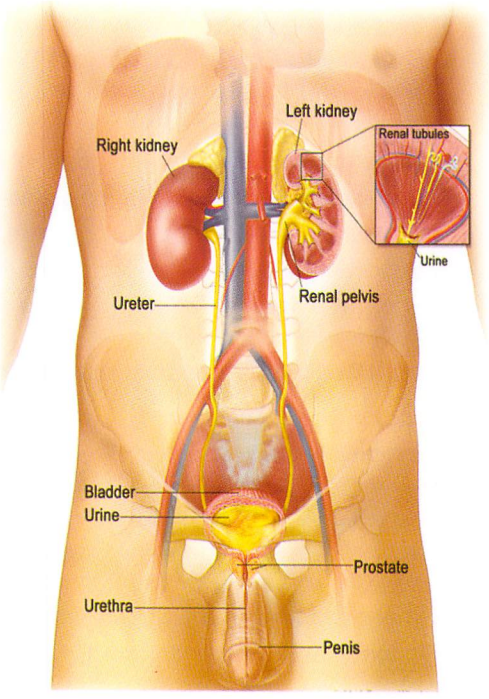
Productive (Wet) Cough

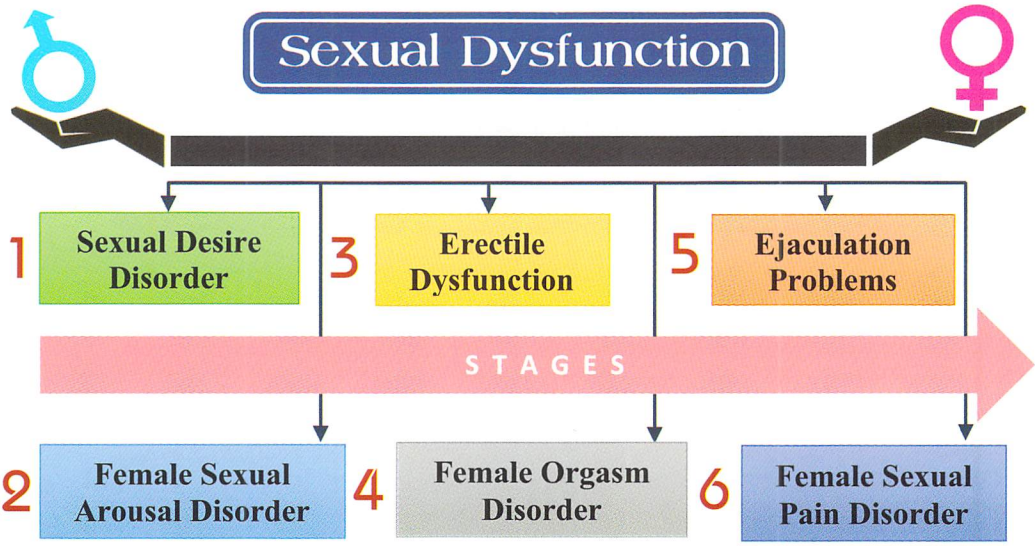
- *Check for*;
  - **COPD**.
  - **Chronic bronchitis**.
  - **Viral** or **bacterial infections**.
- **Expectorants** and **Mucolytics**; - **All-Vent®** (**Bromhexine**, **Terbutaline** and **Guaifenesin**)
  - **Ultrasolv®** (**Carbocysteine**, **Guaifenesin** and **Oxomemazine**).
  - **Toplexil®** (**Oxomemazine** and **Guaifenesin**).
  - **Muco® SR** (**Ambroxol**) - **Mucosol®** (**Carbocisteine**).
- **Herbal Products**; - **Prospan®** or **Ivyrospan®** (**ivy** leaf extract).

Genitourinary (GU)

Subject	No. of page
Drugs for Sexual Dysfunction (Male and Female)	110
Sexual Transmitted Disease (STD) Regimens	119
Drugs for Kidney Stones	121
Drugs for Benign Prostatic Hyperplasia (BPH)	124
Drugs for Urinary Incontinence (UI)	126
Urinary Tract Infections (UTIs)	127
Vaginitis	128







Sexual Dysfunction; is ***difficulty*** *experienced by* an **individual** or a **couple** *during* ***any*** **stage** of a ***normal*** **sexual activity**, including; **libido** (Desire), **arousal**, **erection**, **orgasm** or **ejaculation**.

Sexual Dysfunction ***require*** a ***minimum*** **duration** of *approximately* **6 months**.

Sexual Dysfunction is ***more prevalent*** for **women** (43%) than **men** (31%); 1999 NHSLS

- Sexuality in **adults** *consists of* ***7 components***;
  1) Gender identity; personal conception of oneself as male or female (or rarely; both or neither).
  2) Orientation; heterosexuality (attracted to opposite sex), homosexuality (attracted to one's own sex) and bisexuality (attracted to either sex).
  3) Intention; what a person actually wants to do with his or her sexual partner.
  4) Desire (Libido); driving force that makes think about sex.
  5) Arousal; physiological responses occur in the body and mind as preparation for sexual activity.
  6) Orgasm; sudden discharge of accumulated sexual excitement.
  7) Sexual satisfaction; feel of relaxing and sexual pleasure in last orgasms.

Gender identity, orientation, and intention form sexual identity, whereas desire, arousal, and orgasm are ***components*** *of* **sexual function;**

- Sexual Dysfunction; refers to a ***problem*** *during* ***any*** **phase** of the **sexual response cycle**.

Hormones in Sexual Functions;

- Dopamine (***increase*** **libido**) and Prolactin (***decrease*** **libido**) ***play*** an **important role** to ***control*** **sexual desire** (N.B.; Dopamine ***directly inhibits*** Prolactin ***release*** from the **pituitary gland**).
- Testosterone (***increase*** **libido**) in **men** and **women** ***play*** an **important role** ***control*** **sexual desire** (woman's testosterone levels rise gradually and reach to highest level in ovulation days, and during this period the woman's desire for sex increases).
- Estrogen, Progesterone and Norepinephrine; ***increase*** **libido**.
- Oxytocin (*responsible for* **orgasm** and **sexual pleasure**) and Serotonin; ***decrease*** **libido**.

- **Males** *reach the peak* of their **sex drive** in their **teens** while **females** *reach it* in their **thirties**, then **drops** *slowly* **over** his **lifetime**.

Drugs for Sexual Dysfunction (Male & Female)

1) Hypoactive Sexual Desire Disorder (HSDD)

Hormone Replacement Therapy

Testosterone

Transdermal Testosterone is **used** ***off-label*** for **short-term therapy** to ***increase*** **libido** in **postmenopausal women** (***little evidence*** to ***support*** **long-term use**; longer than 6 months).

Testosterone in **women**, ***may cause*** **weight gain**, **clitoral enlargement**, **acne** and ***excess*** **body hair**.

Estrogen

Local Estrogen therapy in **postmenopausal women** can ***improve*** **clitoral** and **vaginal sensitivity**, ***increase*** **libido** and **arousal**, ***decrease*** **vaginal dryness** and **pain** *during* **intercourse**.

Dehydroepiandrosterone (DHEA)

- **Dehydroepiandrosterone (DHEA)**, *also known as* **Prasterone**, is a ***precursor to*** **Estrogen** and **Testosterone**.
- **DHEA** is ***produced*** in the **adrenal glands**, the **gonads**, and the **brain** (It has important effects in the CNS).
- **DHEA** has been tested for use in many diseases, including **depression**, **osteoporosis**, **lupus**, **menopausal symptoms** (Intrarosa®; vaginal supp) and **other diseases**.

DHEA is *available as* an **OTC supplement** and has been reported to ***increase*** **libido** in **postmenopausal women** (***off-label***); in dose ***less than*** **100 mg/day**.

Female Viagra (Pink Pill)

Flibanserin (Addyi®)# (Flibanorin®) (Flibafemina®)

Flibanserin is the ***first medication*** **approved** (August, 2015) for the ***treatment*** of **Hypoactive Sexual Desire Disorder (HSDD)** in ***pre-menopausal*** **women**.

Flibanserin was ***originally*** *developed as* an ***antidepressant***, ***before*** being **using** for **HSDD**. It is *classified as* a ***multifunctional serotonin agonist antagonist*** (**MSAA**).

- ***Mechanism of action***;
  - **Flibanserin** ***helps restore*** **rebalancing** of **neurotransmitters** that ***influence*** **sexual desire**.
  - **Flibanserin** ***act as*** **5-HT$_{1A}$** ***agonist*** and **5-HT$_{2A}$** ***antagonist*** → ***increases*** **Dopamine** and **Norepinephrine** (both responsible for sexual excitement) and ***decreasing*** **Serotonin** (responsible for sexual inhibition).

Dose; **100 mg orally once** ***per*** **day** at **bedtime** (discontinue after 8 weeks if no response).

Most common side effects; **dizziness**, **nausea**, **fatigue**, **sedation** or **insomnia** and **hypotension**.

FDA ***warning***;

- **Flibanserin** + **Alcohol** ***intake increases*** the **risk** of ***severe*** **hypotension** and **syncope**.
- ***Contraindicated*** with *strong* or *moderate* **CYP3A4 Inhibitors**.
- ***Contraindicated*** in *patients with* **hepatic impairment**.

Other

Bremelanotide (Vyleesi®)

- ***Unlike*** **Sildenafil**, it ***does not*** act by **vasodilatation**, but ***directly*** **increases sexual desire** and **arousal** via ***acting*** in the **brain**.
- ***Mechanism***; ***non-selective*** **agonist** of ***all*** of the **Melanocortin** ***receptors*** *except* MC_2.

Bremelanotide is the ***second medication*** **approved** (FDA *approved* June 21, 2019) for the ***treatment*** of **Hypoactive Sexual Desire Disorder** (**HSDD**) in ***pre-menopausal*** **women**.

- **Dose**; - 1.75 mg SC as needed, at least 45 minutes before anticipated sexual activity.
  - Do not administer >1 dose/24 hr. - >8 doses/month not recommended.

2) Female Sexual Arousal Disorder (FSAD)

Hormone Replacement Therapy

Estrogen

- **Local Estrogen therapy** in **postmenopausal women** can ***improve*** **clitoral** and **vaginal sensitivity**, ***increase*** **libido** and **arousal**, ***decrease*** **vaginal dryness** and **pain**.

Vasodilator

Sildenafil (Viagra®)#

Topical **phosphodiesterase inhibitors** such as **Sildenafil** have been shown to have ***limited benefit*** in **women** with **sexual arousal disorder**.

Alprostadil (Caverject®)#

- **Alprostadil** is a **prostaglandin** E_1 (PGE_1) ***analogue*** used in **male erectile dysfunction** as an **intracavernous** ***injection*** or **urethral** ***suppository***.

Topical **Alprostadil** has been shown to ***increase*** **blood flow** to the **vaginal area** by **vasodilation** and ***shows efficacy*** in **Female Sexual Arousal Disorder** (***off-label***).

- ***Adverse reactions***; **vaginal burning** and **irritation**.

Other

Apomorphine

- **Apomorphine** is a ***dopamine agonists*** that are ***approved for*** the ***treatment of*** **Parkinson's disease**.
- ***Sublingual*** **Apomorphine** (2-3 mg) *thought to* ***enhance*** **sexual response** *due to* **stimuli** in **FSAD**.

Bremelanotide or PT-141

- **Bremelanotide** is ***effective*** in **Female Sexual Arousal Disorder**.

3) Erectile Dysfunction (ED)

- **Erectile dysfunction** (**ED**) or **Impotence**; is a ***persistent*** (at least 6 months) **sexual dysfunction** *characterized by* the ***inability*** to **develop** or **maintain** an **erection** of the **penis** *during* **sexual activity**.
- The ***incidence*** is **low** in **men** *younger than* **40 years** of **age**. **ED** ***affects*** **50%** of **men** ***older than*** **40 years**.
- **Normal Penile Erection**;
  - ***Requirements***; - **Physiological**; **vascular**, **nervous** and **hormonal**.
    - **Psychological**; **sexual stimuli**.
  - ***Mechanism***; - **Reflex erection**; *achieved by* ***directly*** **touching** the **penile shaft**.
    - **Psychogenic erection**; *achieved by* **erotic** or **emotional stimuli**.
  - ***Anatomy***; - ***Two*** **corpora cavernosa** on the ***dorsal side*** → ***fill*** with **blood** → **erection**.
    - ***One*** **corpus spongiosum** on the ***ventral side***.
  - ***Erection Induction***; Sexual stimuli → release of nitric oxide (NO) ☞ **Erection**.
  - ***Erection Maintenance***; ↓ venous outflow from the corpora.

Hormone Replacement Therapy

Testosterone

ONLY **used** *if* **Testosterone** ***levels*** are *found to be* **low**.

Dose and Formulations;

- # **Oral** **Testosterone** ***should not*** be **used** *because* of ***potential*** **liver toxicity**.
- # *Depot* **IM injection** of **Testosterone Enanthate** 200 mg or **Cypionate** 300 mg every 2–3 weeks.
- # **Transdermal patches** (**Androderm®**) ***placed*** **daily** and **Testosterone** **1% gel** (**AndroGel®**) *applied* ***every*** **morning**; ***apply to*** **shoulders**, ***upper*** **arms** ***only*** (*should not be applied to genitals, chest or back*).
- # **Topical solution** (**Axiron®**): ***apply to*** **underarms** ***once daily***.
- # **Pellet implanted** (**Testopel®**); ***provides*** **hormone** for **3–4 months**.
- # **Buccal system** (**Striant®**); *Placed on* **gum tissue** ***twice*** **daily**.

Side effects; ***increase*** **blood pressure**, **acne**, ***enlarged*** **prostate**, **liver** ***toxicity***, **cholesterol** ***changes***, **edema** and **polycythemia**.

Contraindication; **prostate cancer**.

Monitoring; *monitor* **serum** **Testosterone** *within* **1–3 months** and at **6-12 month** ***intervals***.

- *If* ***no improvement*** *after* **3 months**, may ***discontinue*** **treatment**.

Phosphodiesterase Type-5 (PDE5) Inhibitors

Sildenafil (Viagra®)#

Phosphodiesterase type-5 (PDE5) Inhibitor are **First-Line** **drug therapy**.

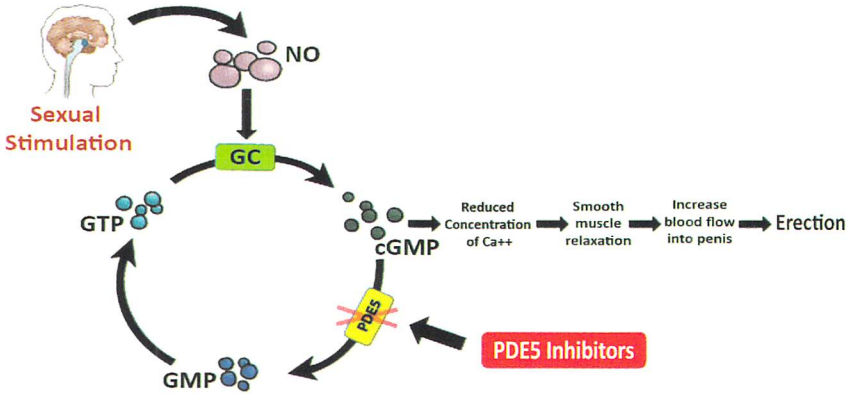
Sildenafil is a ***phosphodiesterase type-5 (PDE5) Inhibitor***.

- **Early 1990s**; **Pfizer** completes *several early* trials of **Sildenafil** citrate for its use as a **heart disease** ***treatment***, but **volunteers** in the clinical trials are *reporting* ***increased*** **erections** several days after taking a dose of the **Sildenafil**.

In 1998 the **FDA approved** **Viagra®** (**Blue pill**) to ***treat*** **Erectile Dysfunction** (**ED**) and **Pulmonary Arterial Hypertension** (**PAH**).

Mechanism of Action;

- **During** **sexual stimulation** ⇨ ***Stimulate*** release of **nitric oxide** (**NO**) in the **corpus cavernosum** in the **penis**.
- **NO** ***release*** ⇨ ***activate*** **guanylate cyclase** (**GC**) ⇨ ↑ **cyclic guanosine monophosphate** (**cGMP**) ⇨ ↓ Ca^{2+} ***influx*** ⇨ ***relaxation*** of **blood vessels smooth muscle** ⇨ **VD** ☞ **Erection**.
- **Phosphodiesterase type-5** ***responsible for*** **degradation** of **cGMP** into **GMP**.
- **Sildenafil** is a ***selective PDE5 Inhibitor*** ⇨ ***accumulation*** of **cGMP** ☞ **Erection**.
- **Sildenafil** has ***no effect*** in **absence** of **sexual stimulation**.



Pharmacokinetics;
- *Absorption*; ***rapidly*** **absorbed** (*orally*).
- *Maximum* **plasma concentrations** *within* **30-120 minutes**.
- *Metabolism*; ***predominantly*** by **CYP3A4**.
- *Excretion*; feces (80%) and urine (13%).

Uses;- **Erectile Dysfunction (ED)**.
- **Pulmonary Arterial Hypertension (PAH)**; It relaxes the arterial wall, leading to decreased pulmonary arterial resistance and pressure.
- **Sildenafil (Respatio®)** can ***improve*** **fetoplacental perfusion** in **pregnancies**.

Dose;
Usual Adult Dose for Pulmonary Hypertension:
- **20 mg** ***orally*** **1*3**.

Usual Adult Dose for Erectile Dysfunction:
- **50-100 mg** ***orally once*** a day, ***as needed***, **1 hour prior** to ***sexual activity***.

Dose *Adjustments* (erectile dysfunction):
- **Geriatric**: **25 mg 1 hour prior** to ***sexual activity***.
- ***Mild*** **to** ***moderate*** **renal dysfunction**: No adjustment recommended.
- **Severe renal dysfunction** (CrCl less than 30 mL/min): 25 mg.
- **Hepatic impairment** (any degree): 25 mg.
- With **alpha blockers** or with **CYP450 3A4 inhibitors** (**Ketoconazole** or **Erythromycin**): 25 mg.

Most Common Side Effects:
- **Headache, flushing, dyspepsia, abnormal vision, nasal congestion, back pain, myalgia, nausea, dizziness** and **rash**.
- **Abnormal vision**: ***due to*** **inhibition** of **PDE-6**.

Contraindications;
In **patients** ***who taking*** **Nitrates**.
Severe **hepatic impairment** *or* ***severe*** **renal impairment**.
Hypotension, ***recent*** **stroke** *or* **heart attack**.
Retinal disorders (genetic disorders of retinal phosphodiesterases).

FDA Warning;
Patients ***should stop*** **Sildenafil** if a **sudden loss of vision** occurs in ***one*** or ***both*** **eyes**, *which could be a sign of* **Non-Arteritic Anterior Ischemic Optic Neuropathy (NAION)**.
Patients ***should stop*** **Sildenafil** in the ***event*** of **sudden** ***decrease*** or ***loss*** of **hearing**.

Vardenafil (Levitra®)# | Tadalafil (Cialis®)#

- **Vardenafil** & **Tadalafil** are ***selective*** **PDE-5 inhibitors** *used for* **Erectile Dysfunction**.
- ***Structurally*** **Vardenafil** is ***similar to*** **Sildenafil**, while **Tadalafil** is ***very different***.
- **Vardenafil** is ***may*** be **effective** in the *treatment of* **Premature Ejaculation**!!

Tadalafil ***used for*** in **treatment of Pulmonary Arterial Hypertension** and ***symptoms of*** **Benign Prostatic Hyperplasia** (**BPH**).

Vardenafil is ***more selective*** than **Sildenafil** and **Tadalafil** to **PDE-5**.

- *Brief comparison*:	Sildenafil	Vardenafil	Tadalafil
FDA approval date	March 27, 1998	August 19, 2003	November 21, 2003
Dosage form	25mg, 50mg, 100mg tablets	2.5mg, 5mg, 10mg, 20mg tablets	5mg, 10mg, 20mg tablets
Efficacy	82-84%	80%	81%
Onset of action	30 minutes (effect delayed by food)	25 minutes (effect delayed by fatty meal)	16-45 minutes (effect NOT delayed by food)
Recommended dose	50 mg, may be adjusted to 100 mg or 25 mg	10 mg, may be adjusted to 20 mg	10 mg, may be adjusted to 20 mg
Duration of action	4 to 5 hours	4 to 5 hours	36 hours
Food Interactions	- Less effective after high-fat meal	- Less effective after high-fat meal - Moderate-fat meal does not reduce its effectiveness	- Works without regard to what eat
Most common side effects	Facial flushing, headache, indigestion	Facial flushing, headache	Headache, indigestion
Less common side effects	Altered vision, dizziness, nasal congestion	Indigestion, nausea, dizziness, nasal congestion	Back pain, muscle aches, nasal congestion, facial flushing, dizziness

Vardenafil is ***also available*** in an **Orally Disintegrating Tablets** (**ODT**); ***not*** **affected by high-fat meals** *with* ***fast*** **onset of action**. (**Levitra® ODT**) (**Staxyn®**).

Avanafil (Stendra®)# (Erovanafile®) (Avanjoy®)

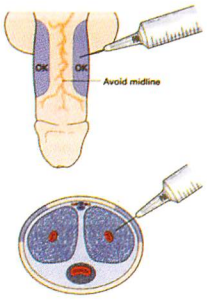
- **Avanafil** is a ***selective*** is a **PDE-5 inhibitor** *approved for* **Erectile Dysfunction** by **FDA** on April 27, 2012.

Onset of action: **15 minutes** (***Fast onset of action***).
Duration of action: ***up to*** **6 hours**.
Dosage form: ***Tablets***: **50**, **100** and **200 mg**.
Side effects *same as* **Sildenafil**.

Prostaglandin Analogues

Alprostadil (Caverject®)#

#Alprostadil is a prostaglandin E_1 (PGE_1) *analogue* used in male erectile dysfunction (*second-line therapy if* PDE-5 inhibitors *fail*), *increases* cAMP → smooth muscle *relaxation*.



Dosage form: urethral suppositories and injection.

MUSE® penile suppository; 125–1000 mcg *inserted into* the urethra.

Caverject®; 2.5-40 mcg injected *directly into* corpus cavernosum.

Onset of action: 5-10 minutes.

Duration of action: *Injection* ⇨ 1-3 hours, *supp.*⇨ 30-60 min.

Common side effects: penile pain (*place of injection*) or urethral pain (*suppository only*), priapism and hypotension.

Priapism; erect penis *does not* return to its flaccid state, *potentially* painful and is *considered* a medical emergency; Phenylephrine, Pseudoephedrine, Terbutaline & Methylene blue can be used.

- *Drug interactions*: *Not used with* PDE inhibitors.

Topical Alprostadil cream (Vitaros®) has been *approved in* Canada as a *first-line treatment* ED.

Other (*off-label*)

Yohimbine (Yohimbex®)

- Yohimbine is a *selective competitive* α_2-blocker, *derived from* bark of *yohimbe* tree.

Uses: mydriatic, erectile dysfunction & fat burner (*promoting* lipolysis; Lipo-6®).

Dose; 5.4 mg orally 3 times daily.

Common side effects: Tachycardia, hypertension, *increased* motor activity, tremor & dizziness

- In 1983, Penile erection could be *induced by* the *Intracavernosal injection* of vasoactive drugs such as Papaverine, Phentolamine and Phenoxybenzamine.

Papaverine (Papacon®)

Papaverine is an *opium alkaloid* antispasmodic drug, *used primarily* in the *treatment* of visceral spasm, vasospasm and in the *treatment* of erectile dysfunction.

- *Mechanism* (not clear); Papaverine is a *non-specific* phosphodiesterase inhibitor.

Papaverine *injection* (Intracavernosal) and topical gel is *also* available.

- *Dose*; 7.5-60 mg Intracavernosal injection.

- *Common side effects*: Priapism, corporal fibrosis, hypotension and hepatotoxicity.

Phentolamine (Rogitine®)

- Phentolamine are non-selective *reversible competitive* α-antagonist.

- *Administration*; intracavernosal injection.

- Phentolamine *monotherapy* is *avoided* because large doses are *required* for an erection, and at these large doses can cause *systemic* hypotension.

- *Common side effects*: Priapism, corporal fibrosis and hypotension.

Apomorphine (Ixense®) (Uprima®)

- *Sublingual* Apomorphine has *demonstrated* some *benefit* in erectile dysfunction.

4) Premature (Early) Ejaculation (PE)

Topical Desensitizing

Lidocaine/Prilocaine (EMLA®)#

Topical desensitizing products ***applied*** to the **penis** *about* **20–30 minutes** *before* **intercourse**.
Condom *can* **used** *to* ***minimize*** the **effect** of the **cream** on **vaginal** ***sensation***.
Side effects; **Hypoanaesthesia** of the **penile shaft** and **vaginal numbness** (if a condom is not used or not adequately washed off the penis).
Contraindications; **man** or ***his*** **partner** has an **allergy** to **product component**.

Antidepressants

The ***most effective*** **pharmacologic therapy** for **premature ejaculation** is **selective serotonin reuptake inhibitors** (**SSRIs**).
- ***Some*** **tricyclic antidepressants** (**TCAs**) have the ***same*** **effect** of **SSRIs**, but have ***more*** **side effects**.
- **Ejaculatory** *delay* to **6–20 times** ***greater than*** *before* **medication**.

Clomipramine (Anafranil®)#

Clomipramine is a ***tricyclic antidepressants***.
Dose; - **Daily Therapy**; **25-50 mg/day**.
- **On-demand Therapy** (*before* **sexual activities**); **25 mg 4-24 hours**.
Clomipramine is ***more effective*** for **premature ejaculation** *than* ***many*** **SSRIs**.
Clomipramine now, it *has* ***largely*** been ***replaced by*** **SSRIs** *because* it is ***side effects***; **hypotension, fatigue, dizziness, dry mouth** and **QT prolongation**.

Paroxetine (Seroxat®)#	Sertraline (Lustral®)#
Fluoxetine (Prozac®)#	Escitalopram (Cipralex®)#

SSRIs may be **used** to ***treat*** **premature ejaculation**, **patients** *may* **report symptom** ***improvement*** *within* a **few days** of ***starting*** **therapy**, with ***best*** **effects** noted ***after*** about **4 weeks** of **treatment**.
Mechanism (*unclear*); ***probably*** **revolves** *around* ***activation*** of the **5-HT$_{2C}$ receptor**.
- ***Dose***; - **Paroxetine**; ***Daily***; **10-40 mg/day**. ***On-demand***; **20 mg 3-4 hr** *before* **sexual activities**.
- **Sertraline**; ***Daily***; **25-200 mg/day**. ***On-demand***; **50 mg 4-8 hr** *before* **sexual activities**.
- **Fluoxetine**; ***Daily***; **5-20 mg/day**. - **Escitalopram**; ***Daily***; **20-40 mg/day**.
Side effects; **GI side effects, headache, anxiety, fatigue**, and **sleep disturbances**.
Mild **erectile dysfunction**, ***reduced*** **libido** and ***increased*** **suicide risks** may occur with ***high*** **doses** and ***long-term*** **use** of **SSRIs**.

Dapoxetine (Priligy®)# (Joybox®) (Durjoy®) >>

Dapoxetine is a ***short-acting*** **SSRI** and it was the ***first*** **drug** ***developed*** **specially** for the ***treatment*** of **premature ejaculation** as an **on-demand therapy**.
Dapoxetine is the ***only*** **approved drug** in the ***treatment*** of **premature ejaculation**, in ***many*** **countries** (***not approved*** **in US**).
Dapoxetine is the **Ideal Compound** for the ***treatment of*** **premature ejaculation**, ***because*** it has a **unique pharmacokinetic profile**; ***rapid*** **absorption**, ***adequate*** **availability** at the **target site**, and ***rapid*** **elimination** and ***minimize*** the *incidence* of **side-effects**.
Dose; **30-60 mg 1-3 hours** *before* **sexual activities** (**on-demand** ***only***).
Some studies have demonstrated that ***combining*** **PDE-5 inhibitors** *with* **SSRIs** ***provides*** **better results**

Other Agents

Tramadol (Contramal®)#

Tramadol is a **μ receptor** ***agonist*** and **norepinephrine/serotonin reuptake** ***inhibitor***.
Tramadol may be ***prescribed*** when **SSRIs** ***haven't been*** **effective** in ***treatment of*** **premature ejaculation**, but ***can't*** be used in ***combination*** *with* an **SSRI**.
Dose; **50 mg 1-3 hours** *before* **sexual activities** (**on-demand** ***only***).
Tramadol has been ***associated with*** ***misuse*** (***delay*** **ejaculation** and **wakefulness**) and ***abuse***.
Long*-term use** of ***high **doses** will ***cause*** ***dependence*** and a ***withdrawal syndrome***.

Pindolol (Visken®)

- Pindolol is a ***non-selective*** **β-blockers** used in ***combination*** with Paroxetine for **premature ejaculation** ***refractory to*** Paroxetine ***alone***.

5) Retarded (Delayed) Ejaculation (RE)

Amantadine (PK-Merz®)# (Symmetrel®)

- Amantadine has ***benefit*** in ***treating*** **delayed ejaculation** by ***potentiate*** **dopaminergic function**.
- ***Dose***; - **Daily Therapy**; **100-200 mg** *twice* **daily**.
  - **On-demand Therapy**; **100-400 mg/day** *for* **2 days** *before* **sexual activities**.
- ***Side effects***; **Hypotension**, **dizziness** and **insomnia**.

Bupropion (Wellbutrin®)#

- Bupropion is a ***weak*** **norepinephrine-dopamine** ***reuptake*** **inhibitor** (**NDRI**).
- *One* **clinical study** *found* Bupropion SR **150 mg** ***once*** **daily** given for **2 months** to **men** with ***lifelong*** **delayed ejaculation** increased ***overall*** **ejaculation**.
- ***Side effects***; ***increased*** **risk of seizures**, **insomnia**, **anxiety**, **headache**, and ***decreased*** **appetite**.

Buspirone (Buspar®)#

- Buspirone is a ***selective*** **5-HT1A agonist**, which is an **antianxiety agent**.
- Buspirone has ***minimal*** **data supporting** ***its*** use for **delayed ejaculation**.

Yohimbine (Yohimbex®)#

- Yohimbine has been associated with ***improvements*** in **delayed ejaculation**.

Cyproheptadine (Triactin®)#

Cyproheptadine acts as a ***serotonin antagonist*** and ***used*** **off-label** as an **appetite stimulant**.
Cyproheptadine has been associated with ***improvements*** in **delayed ejaculation**.
- ***Dose***; **4-12 mg 3-4 hours** *before* **sexual activities**. ***Side effects***; **drowsiness** and **dizziness**.

Pseudoephedrine

- Pseudoephedrine may be ***used for*** **delayed ejaculation** because of its ***agonistic*** **action** on **α receptors** and its *ability to* ***increase*** **norepinephrine**; ***easy*** **contraction** for **ejaculation**.
- ***Dose***; **60-120 mg 1–2 hours** *before* **sexual activities**.

Oxytocin

- Oxytocin ***plays*** a **role** in ***regulating*** **orgasms** *through* **several pathways**.
- ***Dose***; **24 international units** of ***intranasal*** Oxytocin *just* **minutes** *before* **sexual activities** (quick onset of action) has been suggested for *possible* ***treatment*** of **delayed ejaculation**.

6) Retrograde Ejaculation

Imipramine	Pseudoephedrine	Chlorpheniramine

- ***These*** **medications** *can be* **used** in **retrograde ejaculation**, *because* are ***tighten*** the **bladder neck muscles** and ***prevent*** **semen** from **going** *backwards into* the **bladder**.
- ***Usually*** **taken** *at least* **1–2 hours** *before* **sexual activities**.

Sexual Transmitted Disease (STD) Regimens

Genital Herpes (*Herpes Simplex Virus*; HSV Infection)

- **Treatment**; **2015 STDs Guidelines** *from* **Centers** for **Disease Control** and **Prevention** (**CDC**).
  - **Acyclovir** (**Zovirax**®) **400 mg** orally 1*3 daily for 7–10 days.
  - OR **Acyclovir** (**Zovirax**®) **200 mg** orally 1*5 daily for 7–10 days.
  - OR **Valacyclovir** (**Valtrex**®) **1 g** orally 1*2 daily for 7–10 days.
  - OR **Famciclovir** (**Famvir**®) **250 mg** orally 1*3 daily for 7–10 days.

Syphilis

- **Treatments**; **2015 STDs Guidelines** *from* **Centers** for **Disease Control** and **Prevention** (**CDC**).
  - **Primary syphilis/Secondary syphilis**;
    - **Benzathine Penicillin G**; 2.4 million units IM in a single dose (adults).
    - *If penicillin allergy*: **Doxycycline** 100 mg 1*2 daily or **Tetracycline** 500 mg 1*4 daily for 2 weeks.
  - **Latent syphilis/Tertiary syphilis**
    - **Benzathine Penicillin G** 2.4 million units IM every week for 3 weeks.
    - *If penicillin allergy*: **Doxycycline** 100 mg orally 1*2 or **Tetracycline** 500 mg 1*4 daily for 4 weeks.

Chlamydia Infection

- **Treatments**; **2015 STDs Guidelines** *from* **Centers** for **Disease Control** and **Prevention** (**CDC**).
  - **Azithromycin 1 g** in a ***single dose*** OR **Doxycycline 100 mg *twice* daily** for **7 days**.
  - ***Alternatives***: **Erythromycin base** 500 mg orally 1*4 daily for 7 days OR **Erythromycin ethylsuccinate** 800 mg orally 1*4 daily for 7 days OR **Ofloxacin** 300 mg orally 1*2 daily for 7 days OR **Levofloxacin** 500 mg/day 1*1 for 7 days.
- **Abstain** *from* **sexual intercourse** for *at least* **7 days** and *until* **sexual partners** are ***adequately*** **treated**.

Gonorrhoea (Gonococcal Infection)

- **Treatments**; **2015 STDs Guidelines** *from* **Centers** for **Disease Control** and **Prevention** (**CDC**).
  - ***Uncomplicated*** **gonococcal infections** of **pharynx**, **cervix**, **urethra** and **rectum**;
    - ***Single doses*** of **Ceftriaxone** 250 mg IM **+ Azithromycin 1 g**.
    - ***Alternative***; ***single doses*** of **Cefixime** 400 mg orally **+ Azithromycin 1 g**.
    - ***Allergy*** to **cephalosporins**; ***single doses*** of ***oral*** **Gemifloxacin** 320 mg **+** ***oral*** **Azithromycin 2 g**.
- **Abstain** *from* **sexual intercourse** for *at least* **7 days** and *until* **sexual partners** are ***adequately*** **treated**.

Pelvic Inflammatory Disease (PID)

- **Treatments**; **2015 STDs Guidelines** *from* **Centers** for **Disease Control** and **Prevention** (**CDC**).
  - **Parenteral Regimens**; discontinued 24 hrs after clinical improvement & changed to oral therapy for 14 d
    - **Cefotetan** 2 g IV every 12 hours **+ Doxycycline** 100 mg orally or IV every 12 hours
    - OR **Cefoxitin** 2 g IV every 6 hours **+ Doxycycline** 100 mg orally or IV every 12 hours
    - OR **Clindamycin** 900 mg IV every 8 hours **+ Gentamicin** loading dose IV or IM (2 mg/kg), followed by a maintenance dose (1.5 mg/kg) every 8 hours.
    - ***Alternative***; **Ampicillin/Sulbactam** 3 g IV every 6 hours **+ Doxycycline**100 mg orally or IV /12 hr.
  - **Intramuscular/Oral Regimens**;
    - **Ceftriaxone** 250 mg IM in a ***single dose*** **+ Doxycycline** 100 mg orally twice a day for 14 days ***WITH*** or ***WITHOUT*** **Metronidazole** 500 mg orally twice a day for 14 days.
    - **Cefoxitin** 2 g IM in a ***single dose*** and **Probenecid**, 1 g orally administered concurrently in a ***single dose*** **+ Doxycycline** 100 mg orally twice a day for 14 days ***WITH*** or ***WITHOUT*** **Metronidazole** 500 mg orally twice a day for 14 days.

Bacterial Vaginosis (BV)

- **Treatments**; **2015 STDs Guidelines** *from* **Centers** for **Disease Control** and **Prevention** (**CDC**).
  - ***Non-pregnant women***;
    - **Metronidazole** 500 mg orally twice daily for 7 days.
    - OR **Clindamycin** 2% cream, 1 full applicator intravaginally at bedtime for 7 days.
    - OR **Metronidazole** 0.75% gel one full applicator intravaginally once daily for 5 days.

- *Alternatives*: - Clindamycin ovules 100 mg intravaginally at bedtime for 3 days.
  - OR Clindamycin 300 mg orally twice daily for 7 days.
  - OR Tinidazole 2 g orally once daily for 2 days.
  - OR Tinidazole 1 g orally once daily for 5 days.
- *Pregnant women*;
  - Metronidazole 500 mg orally twice daily for 7 days.
  - OR Metronidazole 250 mg orally three times daily for 7 days.
  - OR Clindamycin 300 mg orally twice daily for 7 days.
- *Do not* use Clindamycin *cream during* pregnancy because of the *increased* risk of preterm deliveries.

Vulvovaginal Candidiasis (Vaginal Thrush)

- Treatments; 2015 STDs Guidelines *from* Centers for Disease Control and Prevention (CDC).
  - *Therapeutic Regimens*;

Drug	Dose	Length of Therapy
Butoconazole	2% cream: 5 g intravaginally	1 dose
Clotrimazole	1% cream: 5 g intravaginally at bedtime	7–14 days
	2% cream: 5 g intravaginally at bedtime	3 days
Miconazole	2% cream: 5 g intravaginally at bedtime	7 days
	4% cream: 5 g intravaginally at bedtime	3 days
	100-mg vaginal suppository at bedtime	7 days
	200-mg vaginal suppository at bedtime	3 days
	1200-mg vaginal suppository	1 dose
Nystatin	100,000-unit vaginal tablet at bedtime	14 days
Terconazole	0.4% cream: 5 g intravaginally at bedtime	7 days
	0.8% cream: 5 g intravaginally at bedtime	3 days
	80-mg vaginal suppository at bedtime	3 days
Tioconazole	6.5% ointment: 5 g intravaginally	1 dose
Fluconazole	150-mg oral tablet	1 dose

  - *Recurrent* vulvovaginal candidiasis (four or *more* episodes a year);
    - *Longer* duration of initial therapy;
      - 7–14 days of topical therapy.
      - 100 150 or 200-mg oral dose of Fluconazole *every* third day for a total of 3 doses.
    - *Maintenance regimen*; Oral Fluconazole 100, 150, or 200 mg/week for 6 months.
  - *Pregnant women*; *Drugs of choice* is topical azole, *applied for* 7 days.

Trichomoniasis

Treatments; 2015 STDs Guidelines *from* Centers for Disease Control and Prevention (CDC).
- Metronidazole 2 g orally in a *single dose* OR Tinidazole 2 g orally in a *single dose*.
- *Alternative*; Metronidazole 500 mg orally twice daily for 7 days.
- *All sexual* partners *should be* treated.

Human Papillomavirus (HPV) infection

- Treatments; 2015 STDs Guidelines *from* Centers for Disease Control and Prevention (CDC).
  - *External Anogenital Warts* (penis, groin, scrotum, vulva, perineum, external anus and perianus);
    - *Patient-Applied*:
      - Imiquimod 3.75% (*every night*) OR 5% (*3 times a week*) once at bedtime, *for up to* 16 weeks
      - OR Podofilox® (Podophyllotoxin) 0.5% solution or gel; twice a day for 3 days, followed by 4 days of no therapy, this cycle can be repeated, as necessary, for up to four cycles.
      - OR Sinecatechins 15% (green-tea extract) ointment; three times daily until complete clearance of warts is achieved (should not be continued for longer than 16 weeks).
    - *Provider-Administered*:
      - Cryotherapy with liquid nitrogen or cryoprobe. - OR Surgical removal.
      - OR Trichloroacetic acid (TCA) or Bichloroacetic acid (BCA) 80%–90% solution.
      - *Alternative*; Podophyllin resin, Interferon, photodynamic therapy, and *topical* Cidofovir.
  - Regimens for Urethral Meatus Warts; Cryotherapy with *liquid nitrogen* OR Surgical removal.
  - Recommended Regimens for Vaginal, Cervical and Intra-anal Warts;
    - Cryotherapy with liquid nitrogen. - OR Surgical removal.
    - OR Trichloroacetic acid (TCA) or Bichloroacetic acid (BCA) 80%–90% solution.
- Podofilox® (Podophyllotoxin), Podophyllin & Sinecatechins *should not* be used *during* pregnancy.

HIV/AIDS and hepatitis are *sexually transmitted disease; see Antiviral agents*

Drugs for Kidney Stones

➢ Classification:-

Kidney stone type	Prevalence	Circumstances	Crystal shape	Color
Calcium oxalate	80%	Acidic urine	Envelope	Black/dark brown
Calcium phosphate	5-10%	Alkaline urine	Amorphous	Dirty white
Uric acid	5-10%	Acidic urine	Diamond or barrel	Yellow/reddish brown
Struvite (Magnesium Ammonium Phosphate)	10-15%	Infections in the kidney (ammonia-producing bacteria)	Coffin-lid	Dirty white
Cystine	1-2%	Cystinosis; genetic disorder	Hexagon	Pink/yellow

➢ Prevention:- *depend on stone type*

Calcium Oxalate Stones

Lifestyle modifications; # # # # # # # PATIENT COUNSELLING # # # # # #

- ***Adequate* fluid intake** (2.5–3 L of fluids per day).
- ***Moderate dietary* calcium *intake***.
- ***Avoid* oxalate *containing* foods**; **spinach**, **rhubarb**, **nuts** and **wheat bran**.
- ***Limit* animal protein**; ***decrease* animal protein *intake*** → **1) *increase* citrate *excretion* 2) *decrease* urate *excretion* 3) *decrease* calcium *excretion***.
- ***Limit* sodium intake**; ***decrease* sodium *intake*** → ***decrease* calcium *excretion***.
  - Check food labels for ingredients and hidden sodium, such as; Monosodium glutamate (MSG), Sodium bicarbonate (baking soda & baking powder), disodium phosphate, sodium alginate and sodium nitrate or nitrite.

Drug therapy;

A) **Thiazide diuretics**; ***Reducing* calciuria** & **stone *recurrence*** (risk for uric acid stones)

B) **Alkalinizing agents**; **Citrate Treatment**

Magnesium Citrate (Epimag®)#	**Potassium Citrate** (Urocit-K®)
Citric Acid or Citrate	

1) **Citrate salts**; are ***metabolized by* liver** and **kidney** and ***produce* Bicarbonate** → ***raise* urine pH** → ***inhibits*** the **formation** and ***growth*** of **CaOx crystals**.
2) **Citrate ion *bind*** with **calcium** in **urine** → **form *soluble* citrate complex** → ***inhibits* formation** and ***growth*** of **calcium crystals**.

- **N.B.**; **Citrate treatment *raise* urine pH**, and this ***may* increase** the ***risk*** for **calcium phosphate stones** if ***urine* calcium *remains* high** and **fluid intake** is ***not maintained***.
- **Citrocid Magnesium Plus®** (**Citric acid** + **Magnesium** + **pyridoxine**); ***Adequate* quantities** of **B-complex vitamins** and **Magnesium** can ***prevent* calcium oxalate stone formation**.

C) **Allopurinol** (**Zyloric®**); ***some* patients** with **calcium oxalate *stones*** have **hyperuricosuria**. **Uric acid *facilitates*** the **precipitation** of **calcium oxalate *crystals***.

Calcium Phosphate Stones

- The ***common cause***; ***high* urine pH (alkaline urine)** and **hypercalciuria**.

Lifestyle modifications; # # # # # # # PATIENT COUNSELLING # # # # # #

- ***Adequate* fluid intake** (2.5–3 L of fluids per day).
- ***Moderate dietary* calcium *intake***. - ***Limit* animal protein** and **sodium intake**.

Drug therapy;

A) **Thiazide diuretics**; ***Reducing*** **calciuria** and **stone** ***recurrence***.

B) **Acidifying urine**; by ***large dose*** of **Vitamin C** (**Vitacid**®); 1 g eff. 1*2 or 1*3

C) **Citrate Therapy**; is ***controversial*** (*not backed by any trials*);

- ***Benefits***; **Citrate** in the **urine** ***forms*** a *soluble* ***complex*** with **Calcium**.
- ***Risk***; **Citrate** ***raise*** **urine pH** (***increase*** **calcium phosphate stone** ***formation***).

Uric Acid Stones

Lifestyle modifications; # # # # # # # # **PATIENT COUNSELLING** # # # # # # #

- ***Adequate*** **fluid intake** (2.5–3 L of fluids per day).
- ***Limit*** **Purine-Rich Foods**;
  - **Organ meats**; Liver, kidneys, brain and heart.
  - **Game** (hunting) **meats**; rabbit and venison.
  - **Fish**; herring, mackerel, sardines and sprats.
  - **Seafood**; mussels, shellfish and caviar.
  - **Yeast extracts**; beer (not wine).
  - **High-fructose foods**.

Drug therapy;

A) **Alkalinizing agents**;

Potassium Sodium Hydrogen Citrate (Uralyt-U®)#

Sodium Citrate + Citric Acid (Bicitra®)

- **Citrates** are ***metabolized by*** **liver** and **kidney** and ***produce*** **Bicarbonate** → ***raise*** **urine pH** → **dissolve and** ***inhibits*** the **formation** and ***growth*** of **Uric Acids crystals**.

Piperazine Citrate (Urosolvine®)#

- **Urosolvine**® effervescent; introduced in 1949; contains **Piperazine** ***anthelmintic agent***; increase the solubility of urates, **Colchicine**; brings rapid relief in cases of acute gout attacks and **Atropine**; relieves spasms of the urinary tract.

B) **Allopurinol** (**Zyloric**®); ***decrease*** **Uric Acid** **production** by ***competitively inhibiting*** **xanthine**

Renal Colic Managements

Pain Management

NSAIDs

Diclofenac (**Voltaren**®) (**Cataflam**®) is often the **FIRST CHOICE** **NSAID** for **renal colic**.

Dose; **Diclofenac** **75 mg** (3 mL) **injection**, **IM**, ***repeated once*** (***may be given*** **30 minutes** later ***if required***, in the ***opposite side***).

May also be ***combined with*** **oral** **Diclofenac** to a ***maximum*** of **150 mg**, daily, for a ***maximum*** of **two days**. **Oral** or **rectal** **Diclofenac**, **75-150 mg**, **daily**, ***can be*** **prescribed**.

Diclofenac is ***contraindicated*** in **patients** who have a **cardiovascular risk**. ***Other*** **NSAIDs**, e.g. **Ibuprofen** or **Naproxen**, ***should*** *provide* **effective pain management** for ***patients*** with **renal colic** in ***these*** **situations**.

Opioids

Morphine 5-10 mg, IM *every* 4 hours; is an ***alternative* treatment** to **NSAIDs**.
Morphine is ***preferred* over NSAIDs** in **pregnant women**.

Antiemetic Therapy

Metoclopramide (Primperan®) is the ***only* antiemetic** that has ***been* specifically studied** in the ***treatment*** of **renal colic**, ***usual* adult *dose*** is **10 mg IV** or **IM *every* 4-6 hours** as ***needed***.

Antispasmodic Therapy

Antispasmodic *most commonly* in ***combination*** *with* **pain management agents**.
Hyoscine N-butylbromide (Buscopan®) ***reduces* amount** of **opioids *required*** in **renal colic**.
Drotaverine (Do-Spa®) is an **antispasmodic *without* antimuscarinic *adverse effects***.
- **Aminophylline** is a ***methylxanthine***, it ***relaxes* smooth muscles**.

Medical Expulsive Therapy (MET)

- **MET** is ***useful for* stones diameter *less than* 10 mm**.
- **MET**; ***includes* α-blockers, Calcium Channel Blockers, Corticosteroids** and **Phosphodiesterase-5 (PDE5) Inhibitors**.
- **NSAIDs *have* ureteral-relaxing effects** and *can be* **considered** a ***form of* MET**.

* **α-blockers**; **Tamsulosin (Flomax®)** is a ***selective* α_{1A} receptor *antagonist*** *making it* the ***most commonly*** *prescribed* **α- blocker**, **Silodosin (Rapaflo®)** is *another* ***selective* α_{1A} receptor *antagonist*** can be **used**.
* **Calcium Channel Blockers**; **Nifedipine (Epilat®)** is the ***only* calcium channel blocker** that has ***shown*** *some* **benefit** in **stone expulsion** (**Tamsulosin *better than* Nifedipine**).
* **Corticosteroids**; have been *reported to* ***facilitate* stone expulsion**.
* **Phosphodiesterase-5 (PDE5) Inhibitors**; ***Relaxing* effects** of **ureteral muscle tension** have been observed in patients ***receiving* Vardenafil (Levitra®), Sildenafil (Viagra®)** and **Tadalafil (Cialis®)**.

Miscellaneous Agents

* **Antibiotics**; can be **used** if ***infections*** are **present**, *such as*;
  - **Ciprofloxacin (Cipro®)** and **Sulfamethoxazole/Trimethoprim (Septrin®)**
* **Urinary Tract Antiseptics**; can be **used** if ***infections*** are **present**, *such as*;
  - **Nitrofurantoin (Uvamin®)** ***concentrated*** in the **urine**, *leading to* ***higher*** and ***more* effective levels** in the **urinary tract**, it works by ***damaging* bacterial DNA**.
  - **Hexamine *decomposes*** at an **acidic pH** to form **formaldehyde** and **ammonia**, and the **formaldehyde** is ***bactericidal***.
* **Other Agents**;
  # **Halphabarol (Proximol®)** (*Cymbopogen proximus*) (Halfa bar); is an ***antispasmodic*** and ***used widely*** in **management** of **renal colic**.
  # **Khellin** (*Ammi Visnaga*); *work by* ***decrease* calcium oxalate stone *formation***, **antibacterial *activity***, ***antispasmodic*** and ***acting as*** a **diuretic**.
  # **Cystone®**; *work by* ***decrease* kidney stone *formation***, **antibacterial *activity***, ***antispasmodic*** and ***acting as*** a **diuretic**.
  # **Rowatinex®**; *work by* **urinary muscle *relaxant***, ***facilitating* ureteral stone *passage*** and ***decrease* calcium oxalate stone *formation***.

Drugs for Benign Prostatic Hyperplasia (BPH)

Lower Urinary Tract Symptoms (LUTS); *group of* **medical symptoms** *caused mainly by*; benign **prostatic hyperplasia (BPH)**, **urinary tract infection (UTI)** and **chronic prostatitis**.

A) Storage (Irritative) Symptoms;

- **Urinary frequency**; increased frequency of urination.
- **Urinary urgency**; increased urgency of urination.
- **Dysuria**; painful urination.
- **Nocturia**; excessive passage of urine at night.

B) Voiding (Obstructive) Symptoms;

- **Poor stream** (unimproved by straining); decreased force.
- **Hesitancy** (worsened if bladder is very full); a delay between trying to urinate and the flow actually beginning.
- **Dribbling**; loss of small amounts of urine due to a poor urinary stream.

- ***N.B.***; **LUTS** as an ***independent*** **risk factor** for **erectile dysfunction** and **ejaculatory dysfunction**.

Medication can cause LUTS;

- **α-Adrenergic agonists**; ***Decongestants*** and **Pseudoephedrine**.
- **Anticholinergics**; **Antispasmodics**, **Antihistamines**, **Tricyclic Antidepressants** and **Phenothiazines**.
- **Diuretics**.
- **Testosterone**.

Benign Prostatic Hyperplasia (BPH) or **Benign Prostatic Hypertrophy**; is a ***noncancerous*** *increase* in **size** of the **prostate**, is a ***common*** in **older men**.

➢ BPH Managements:-

1) Watchful Waiting

- **Watchful waiting** is ***recommended*** in **men** who have **mild symptoms**.

2) α_1-Receptor Antagonists

Prazosin (Minipress®)#	**Doxazosin** (Cardura®)#	**Terazosin** (Hytrin®)
Alfuzosin (Xatral®)#	**Tamsulosin** (Flomax®)# (Omnic-Ocas®)#	**Silodosin** (Rapaflo®)

- **Prazosin**, **Doxazosin** and **Terazosin** are a ***non-specific selective*** **α_1 blocker**; ***acts on*** **blood vessels** (lower blood pressure) and **prostate** (relax prostate and urethra muscles and relax bladder neck), ***used in*** **symptoms of BPH (LUTS)** and **hypertension**.

Alfuzosin is a ***specific selective*** **α_1 blocker** in the **prostate** and **bladder**, ***approved only*** for **symptoms of BPH (LUTS)**, ***not indicated*** for the **treatment** of **hypertension**.

Tamsulosin and **Silodosin** are a ***specific selective*** **α_1 blocker** that has ***preferential selectivity*** for *the* **α_{1A} receptor** in the **prostate** *versus* the **α_{1B} receptor** in the **blood vessels** ***approved only*** for **symptoms of BPH (LUTS)**, ***not indicated*** for the **treatment** of **hypertension**.

All **α-blockers** ***relieve*** **symptoms** in **men** ***with*** **moderate** to **severe BPH**.

Side effects;

- ***All*** **α-blockers** can ***cause*** **orthostatic hypotension** (non-specific >>> specific); Therapy with ***non-specific*** **agents** ***should*** begin at a **low dose** and then be ***titrated*** **upward**. **Sildenafil** (or ***other*** **PDE-5**) in doses ***greater than*** **25 mg** should not be taken ***within*** **four hours** of **alpha-blocker** use.
- ***All*** **α-blockers** can ***cause*** **ejaculation changes**, **headaches**, **nasal congestion** and **weakness**.
- **Patients** ***taking*** **Tamsulosin** are prone to a ***complication known*** as **floppy iris syndrome** during **cataract surgery**, ***should avoid*** *until* their **cataract surgery** is **completed**.

Doses;

Prazosin	***Start*** at 1 mg twice daily; ***usual*** 2–10 mg in two to three divided doses.
Doxazosin	***Start*** at 1 mg daily; ***usual*** 1–4 mg daily; ***maximum*** 8 mg.
Terazosin	***Start*** with 1 mg taken at bedtime; ***usual*** 1–10 mg daily; ***maximum*** 20 mg.
Alfuzosin	10 mg daily as a single dose.
Tamsulosin	0.4–0.8 mg daily as a single dose.
Silodosin	8 mg daily as a single dose - 4 mg daily if CrCl 30–50 mL/minute.

Drug interactions; *All* **α-blockers** are ***metabolized through*** the **CYP3A4** ***pathway*** and have **drug** ***interactions*** with ***strong*** **CYP3A4 inhibitors** and **inducers**.

3) 5-α-Reductase Inhibitors

Finasteride (Proscar®)# | **Dutasteride** (Avodart®)#

Finasteride and **Dutasteride** are a ***5-α-reductase inhibitors***.
- They inhibits ***5α-reductase enzyme*** which ***convert*** **Testosterone** into the ***more potent androgen*** **Dihydrotestosterone (DHT)**; *lead to* ↓ **prostate size** & ↑ **urinary flow**.

Most beneficial; in **men** *with* **prostates** ***larger than*** **40 g**.
Should not use in **men** *with* **LUTS** ***secondary*** to **BPH** ***without*** **prostatic enlargement**.
Onset of benefits; *approximately* **6 months** of **therapy**.
Doses; **Finasteride**; 5 mg daily. - **Dutasteride**; 0.5 mg daily.
Side effects; ***decreased*** **libido**, **ejaculatory problems** and **erectile dysfunction**.

4) Combination Therapy

Dutasteride + Tamsulosin (CombAT®) (Duodart®) (Jalyn®) (Combodart®)

It contains; **Tamsulosin** 0.4 mg + **Dutasteride** 0.5 mg.
Indications; **severe symptoms** of **BPH** in **enlarged prostate** ***larger than*** **40 g**.

5) Phosphodiesterase Type-5 (PDE5) Inhibitors

Tadalafil (Cialis®)#

Tadalafil are ***selective*** **PDE-5 inhibitors** *used for* **Erectile Dysfunction** and it is ***approved for*** use in **BPH** in **2011** or ***both*** **BPH** and **Erectile Dysfunction**.
- ***Mechanism*** (*exact mechanism unknown*).
- ***Doses***; 5 mg once daily. ***Combination of*** **Tadalafil** and **α_1-blockers** is a ***risk of*** **hypotension** ***but*** it can **safe** in **proper instructions**.

6) Antimuscarinics

Oxybutynin (Ditropan®)# (Uripan®)#

Tolterodine (Detrusitol®)# | **Solifenacin** (Sofenacin®)#

- ***Used*** to ***improve*** **irritative voiding symptoms** (e.g., **urinary frequency**, **urgency**), which **α_1-blockers** and **5-α-reductase inhibitor** ***does not improve*** **these symptoms**.

7) Phytotherapy or Alternative Therapy

(Pepon®)# (Lycomen®)# (ProstaCure®)#

- **Saw Palmetto** (*Serenoa repens*) **extract**; ***most commonly used*** and ***studied***; ***mild*** to ***moderate*** **improvement** in **LUTS**; some of urologists preferred **saw palmetto** over pharmacotherapy.
- **Stinging nettle** (*Urtica dioica*), **South African stargrass** (*Hypoxis rooperi*), **pumpkin seed** (*Cucurbita pepo*), and **African plum** (*Pygeum africanum*); *can be used*, but the **AUA** ***does not*** **recommend** the *use of* **Phytotherapy**.

8) Surgery

Surgery is ***preferred*** in **men** ***with*** **severe symptoms** and in those ***with*** **moderate symptoms** who have ***not adequately*** **responded** to **medical options**.

Drugs for Urinary Incontinence (UI)

Antimuscarinics

Oxybutynin (Ditropan®)# (Uripan®)#	**Tolterodine** (Detrusitol®)#
Solifenacin (Sofenacin®)#	**Flavoxate** (Genurin S.F®)#
Trospium (Spasmolyt®)	**Propiverine** (Mictonorm®)

- **Anticholinergic Drugs**; **Oxybutynin**, **Tolterodine**, **Fesoterodine**, **Trospium**, **Solifenacin** and **Darifenacin**; They ***reduce*** **detrusor over-activity** by ***antagonizing*** **M_3 muscarinic receptors** in the **bladder**. ***Longer*-acting formulations** may be ***better*** **tolerated**.

Oxybutynin & **Tolterodine** are ***most commonly used***.

Oxybutynin is available as a transdermal system (topical patches).

Fesoterodine is a ***prodrug***. It is broken down into its **Tolterodine**.

Solifenacin by CYP3A4 ⇨ ***drug interaction***; with ***LME inhibitors***. May also ***prolong the QT interval*** ⇨ ***Contraindicated*** in patient with ***long QT interval***.

Flavoxate is ***indicated for*** symptomatic relief of **interstitial cystitis**, dysuria, urgency, nocturia, supra-pubic pain, frequency and incontinence as may occur in **cystitis**, **prostatitis** and **urethritis**, **urethrocystitis/urethrotrigonitis**.

- **Trospium** ***should be*** **taken** ***at least*** **1 hour** ***before*** **meals** or *given on* an **empty stomach**.

Emepronium may cause **ulceration of oesophagus**, so it ***should be taken*** in **orthostatic position** ***with sufficient*** **amounts** of **liquids**.

Antidiuretic Hormone (ADH)

Desmopressin (Minirin®)#

Desmopressin is a ***synthetic*** **replacement** for **antidiuretic hormone** (**ADH**) or **vasopressin**, the **hormone** that ***reduces*** **urine** ***production*** *during* **sleep**.

Desmopressin is the ***first-line treatment*** for **enuresis** in **children** ***older than*** **5 years**.

Dose; in **Nocturnal enuresis**.

- # **Minirin®**; **Regular tablets**; 0.2 mg one hour before bedtime, if needed after 10 to 14 days, the dose may be increased by 0.2 mg to a maximum dose of 0.6 mg.
- # **Minirin®-melt**; **Oral melt tablets**; 120 µg sublingual are given 30 to 60 minutes before bedtime; if needed after 10 to 14 days, the dose may be increased by 120 µg to a maximum dose of 360 µg.

Uses; **Nocturnal enuresis**, **coagulation disorders** and **central diabetes insipidus**.

Side effects; **Nausea**, **headaches**, **flushing**, **hyponatremia** and **seizures**.

β_3-Agonist

Mirabegron (Myrbetriq®)# (Betmiga®)# (Bladogra®)

Mirabegron; ***approved by*** the **FDA** in **2012**, **Mirabegron** act on **β_3-adrenergic receptors** to ***relax*** the **detrusor**.

Dose; **25-50 mg** ***orally*** **once**.

Common adverse effects are **nausea**, **diarrhea**, **constipation**, **dizziness**, and **headache**. ***Increased*** **blood pressure** ***can*** **also** *occur*, and **Mirabegron** ***should not*** be used in **patients** with ***uncontrolled*** **hypertension**.

Urinary Tract Infections (UTIs)

- **Urinary Tract Infection** (**UTI**); is an ***infection*** that ***affects*** **part** *of* the **urinary tract**;
  - ***Lower*** **Urinary Tract Infection**; it is known as a **bladder infection** (**cystitis**).
  - ***Upper*** **Urinary Tract Infection**; it is known as **kidney infection** (**pyelonephritis**).
- **UTIs** are ***classified as*** **uncomplicated** and **complicated**;
  - **Uncomplicated** is an **infection** *without* **structural** or **functional** ***abnormalities*** of the **urinary tract**.
- ***Recurrent*** **UTIs are considered** ***either*** ***reinfections*** **or** ***relapses***;
  - **Reinfection** ***usually happens more than*** **2 weeks** ***after*** **the** ***last*** **UTI, and is** ***treated as*** **a new** ***uncomplicated*** **UTI.**
  - **Relapse** ***usually happens within*** **2 weeks of the** ***original*** **infection and is a** ***relapse*** **of the original infection either** ***because*** **of** ***unsuccessful*** **treatment of the original infection, a** ***resistant*** **organism, or anatomical** ***abnormalities.***
- **The** ***most common*** **cause of** ***infection*** **is** ***Escherichia coli.***

Lower UTI (Cystitis)	Upper UTI (Pyelonephritis)
Dysuria	Frequency, dysuria, haematuria
Frequent urination	Suprapubic pain
Urgency	Costovertebral angle tenderness; **flank pain**
Occasionally, gross haematuria	**Fever**, chills
Occasionally, foul-smelling urine	Elevated WBC
	Nausea, vomiting

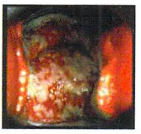
* **Older adults**; may have only nonspecific symptoms, such as mental status changes, abdominal pain, and decreased eating or drinking.

- **Pharmacotherapy** (***Recommendations***);
  - ***Uncomplicated*** **Cystitis**;
    - * **Recommended therapy**;
      - **Trimethoprim/Sulfamethoxazole** **160mg/800mg** ***twice*** **daily** *for* **3 days** (***Avoid*** if **resistance** ***prevalence*** is known to ***exceed*** 20% OR if **used** for **UTI** in *previous* **3 months**).
      - **Nitrofurantoin** **100 mg** ***twice*** **daily** *for* **5 days.**
      - **Fosfomycin** **3 g, one dose.**
    - * **Alternatives**; - **Fluoroquinolones** *for* **3 days** OR **β-Lactams** *for* **3–7 days.**
  - ***Uncomplicated*** **pyelonephritis**;
    - * **Outpatient therapy** (if patient is ***not*** **immunocompromised** or does ***not*** have **nausea** & **vomiting**);
      - **Trimethoprim/Sulfamethoxazole** *for* **14 days.**
      - **Fluoroquinolones** *for* **5–7 days.**
      - **β-Lactams** *for* **10–14 days** (less effective than first two options).
    - * **Uropathogen resistance** (***greater than*** 10%);
      - **Use** ***initial*** **dose** of an **intravenous**;
        - ***Long-acting*** **β-lactams** (e.g., **Ceftriaxone**).
        - ***Once-daily*** **Aminoglycosides.**
  - ***Complicated*** **UTIs**;
    - * **Inpatient therapy**; **Fluoroquinolones**, **Aminoglycosides** OR ***Extended-spectrum*** **β-lactams**; **therapy duration**: **5–14 days** (**5 days** *with* **Levofloxacin**).
  - **UTIs** in **Pregnancy** (pregnant women should be screened for bacteriuria and treated, even if asymptomatic)
    - * **7-day treatment regimen**;
      - **Amoxicillin.**
      - **Nitrofurantoin** (***avoid*** *after* **38 weeks' gestation** and ***during*** **labor** and **delivery**).
      - **Cephalexin.**
    - * **Antibiotics to avoid**; **Fluoroquinolones**, **Tetracyclines**, **Aminoglycosides** and **Trimethoprim/Sulfamethoxazole** (used frequently but avoidance recommended, especially during the late third trimester).

Vaginitis

- **Vaginitis** is ***inflammation*** of the **vagina**.
- **Vulvovaginitis**, is an ***inflammation*** of the **vagina** and **vulva**.
- ***Diagnosis*** *based on* ***presence*** of ***abnormal*** **discharge**, **vulvovaginal discomfort (irritation)** or **both**.
- It is ***usually*** *due to* **infection**; **bacterial vaginosis** is the ***most common*** **vaginal infection**.
- ***Normal*** **discharge** is *usually* **clear** or **milky** *with* ***no*** **malodor**.
- ***Most Common Symptoms***;
  - **Irritation** or **itching** of the **genital area**.
  - ***Abnormal*** **vaginal discharge** *with* an **unpleasant odor**.
  - **Burning** ***during*** **urination**.
  - **Discomfort** *during* **sexual intercourse**.
- ***Types*** of **Vaginitis**;
  1) **Bacterial Vaginosis**; which results from ***overgrowth*** of ***Gardnerella vaginalis*** and ***decrease growth*** of ***Lactobacillus*** which are normally present in vagina.
  2) **Vulvovaginal Candidiasis**; which results from ***overgrowth*** of a **fungal organisms** *usually* ***Candida albicans***.
  3) **Trichomoniasis**; which is caused by a ***Trichomonas vaginalis*** and is commonly transmitted by sexual intercourse.
  4) **Atrophic Vaginitis** (non-infectious vaginitis); which results from ***reduced*** **Estrogen** levels ***after*** **menopause**.

* **Bacterial Vaginosis** *vs* **Vulvovaginal Candidiasis**;

	1) Bacterial Vaginosis	2) Vulvovaginal Candidiasis
Causes	↑ *Gardnerella vaginalis* ↓ *Lactobacillus*	↑ *Candida albicans*
Risk Factors	- ***New/multiple*** **sex partners**. - Natural ***lack*** of **lactobacilli**. - **Smoking**. - **Vaginal douching**. - **Uses** of **intrauterine device (IUD)**.	- **Antibiotics use**. - ***Increased*** **estrogen levels**. - ***Uncontrolled*** **diabetes**. - **Diet** ***high*** in **refined sugars**. - ***Impaired*** **immune system**. - **Sexual activity**. - **Uses** of **intrauterine device (IUD)**.
Clinical Features	1) **Discharge appearance**; * **Off-white discharge** * **Thin & homogenous** * **Foul-smelling "fishy" vaginal odor** 2) **Symptoms**: *Usually* ***without*** *significant* **Irritation** or **Erythema**.	1) **Discharge appearance**; * **Little/No discharge**, *if* ***present***; * **White & clumpy**. * **Thick** * **Cottage cheese** ***appearance***.  2) **Symptoms**: - **Itching** and **irritation**. - **Redness** and **swelling** of **vulva**. - **Vaginal pain** and **soreness**. - **Dysuria** and **dyspareunia**.
Treatments	- **Metronidazole** (Flagyl®) 500 mg orally twice daily for 7 days. - **OR Clindamycin** (Dalacin®) 2% cream, 1 full applicator intravaginally at bedtime for 7 days. - **OR Clindamycin** (Dalacin®) 300 mg orally twice daily for 7 days.	- **Fluconazole** (Diflucan) 150-mg oral tablet single dose. - **OR Miconazole** (Gyno-Daktarin®) 2% cream: 5 g intravaginally at bedtime for 7 days. - **OR Miconazole** (Gynozol® 200 MG) vaginal suppository at bedtime for 3 days.

- Home remedies for *recurrent* vulvovaginal candidiasis (four or *more* episodes a year);
  - *Daily* intake of yogurt (*containing* live *Lactobacillus acidophilus*).
  - *Eliminate* use of nylon or tight-fitting clothing.
  - Consider *discontinuing* oral contraceptive.
  - *Improve* glycemic control in diabetic patient.

3) Trichomoniasis

Definition
- **Trichomoniasis** is a ***sexually transmitted*** **infection** that in **women** can cause a ***foul-smelling*** **vaginal discharge**, **genital itching** and **painful urination**.
- **Men** who have **trichomoniasis** ***typically*** have **no symptoms**.
- **Pregnant women** who have **trichomoniasis** are at ***higher risk*** of **delivering prematurely**.

Causes
- ***Trichomonas vaginalis***; is an **anaerobic**, **flagellated protozoan**, a form of **microorganism**.

Clinical Features

1) **Discharge appearance**;
   * **Profuse**, **frothy** and **watery** (**Thin**).
   * **Malodorous**.
   * **Yellow-green discharge**.

Strawberry cervix

2) **Symptoms**;
   - **Itching** and **irritation**.
   - **Redness** and **swelling** of the **vulva**.
   - **Vaginal pain** and **soreness**.
   - **Dysuria** and **dyspareunia.**

Treatments
- **Metronidazole** (Flagyl®) 2 g orally in a ***single dose***
- **OR Tinidazole** (Protozole®) - (Faisigyn®) 2 g orally in a ***single dose***.

4) Atrophic Vaginitis (Vaginal Dryness)

Definition
- **Atrophic vaginitis** is an ***inflammation*** of the **vagina** due to the ***thinning*** and ***shrinking*** of the **tissues**, as well as ***decreased*** **lubrication** (***non***-**infectious vaginitis**).

Causes
- **Vaginal atrophy** is *caused by* ***decrease*** in **Estrogen** ***production***.
- ***Less*** **Estrogen** makes **vaginal tissues** ***thinner***, ***drier***, ***less*** **elastic** and ***more*** **fragile**.

Risk Factors
- ***After*** **menopause**.
- ***Other conditions*** *associated with* **estrogen** ***deficiency***.
- **Oophorectomy** (surgical removal of ovaries).
- **Radiation and chemotherapy therapy**.
- **Immunologic disorders**.
- **Premature ovarian** ***failure***.
- **Endocrine disorders**.
- **Antiestrogen medications**.

Clinical Features

1) **Discharge appearance**; ***No*** **abnormal discharge**.
2) **Symptoms**; - **Vaginal dryness** and **burning**.
   - **Dysuria** (burning with urination).
   - **Dyspareunia** (painful sexual intercourse).
   - ***More*** **urinary tract infections**.
   - ***Light*** **bleeding after intercourse**.
   - ***Decreased*** **vaginal lubrication** ***during*** **sexual activity**.

Treatments

A) **Hormone Replacement Therapy** (**HRT**); ***all*** **routes** of **Estrogen delivery** ***relieve*** the **symptoms** of **atrophic vaginitis**.

B) **Vaginal Lubricant** (K-Y® gel - Durex®); ↓ **discomfort** ***during*** **sexual intercourse**.

Musculoskeletal

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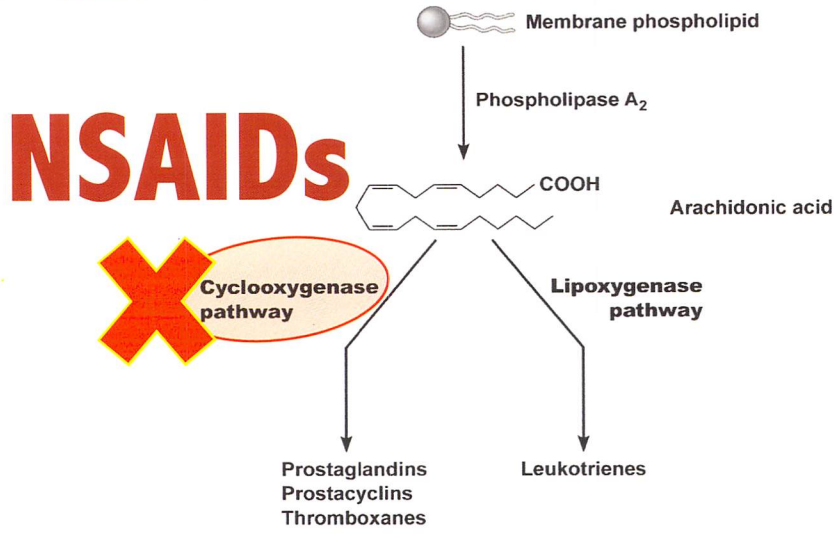
Pain Management

Pain can be **either** **acute** or **chronic** and is a consequence of **complex neurochemical processes** in the **peripheral** and **central nervous systems (CNS)**.
- **Analgesic** or **painkiller** is *any group* of drugs used to ***achieve*** **analgesia**, ***relief from*** **pain**
Types of pain;
  - ***According to duration***;
    - **Acute pain**; ***less than*** **30 days**.
    - **Chronic pain**; ***more than*** **6 months**.
    - **Subacute pain**; ***from*** **1-6 months**.
  - ***According to type of damage***;
    - **Nociceptive pain**; ***tissue damage***; skin, muscles, visceral organs, joints, tendons, or bones.
    - **Neuropathic pain**; ***nerve damage***; spinal cord injury, multiple sclerosis and diabetic neuropathy.
- **Breakthrough pain**; ***just occurs***, *without* any ***obvious*** **trigger**; type of cancer pain.
Analgesic choice is also ***determined by*** the **type of pain**; **for example**;
  - **Mild** to **moderate pain**; **Simple** (non-opioid) **analgesics** **such as nonsteroidal anti-inflammatory drugs (NSAIDs)** are **often effective**.
  - **Neuropathic pain**; **Responds** ***best*** to **anticonvulsants** and **tricyclic antidepressants**.
  - **Severe** or **chronic malignant** or **non-malignant pain**; **Opioid analgesics** are considered **part** of the **treatment plan** in select patients.
Major Classes of Analgesics;
  - **NSAIDs** and **Paracetamol**.
  - **Opioid Analgesics**; **Agents** that **produce morphine-like effect**.
  - **Specific agents**; **Anticonvulsants** and **tricyclic antidepressants**.

Non-steroidal Anti-inflammatory Drugs (NSAIDs)

NSAIDs; are a ***group*** of **chemically** ***dissimilar*** **agents** that ***have*** **analgesic** (*pain-killing*) and **antipyretic** (*fever-reducing*) and **anti-inflammatory** ***effects***.
Paracetamol (**Acetaminophen**) is ***generally*** ***not*** **considered** an **NSAID** because *it has* ***only*** ***little*** **anti-inflammatory activity**.
The **NSAIDs** *act by* ***inhibiting*** the **synthesis** of **prostaglandins**.



Major Roles of Eicosanoids;
- **Prostaglandins (PGs)**;
  - ***Modulate* pain, inflammation and fever.**
  - ***Control* acid secretion and mucus production** *in the GIT.*
  - ***Control* renal blood flow.**
  - ***Control* uterine contractions.**
- **Prostacyclin (PGI_2)**;
  - ***Inhibit* platelet aggregation.**
  - ***Induce* vasodilation.**
- **Thromboxane-A_2 (TXA_2)**;
  - ***Induce* platelet aggregation.**
  - ***Induce* vasoconstriction.**
- **Leukotrienes (LTs)**;
  - ***Powerful* bronchoconstriction.**
  - ***Increase* vascular permeability.**

- PGI_2 & PGE_1; ↓ platelet aggregation & VD
- PGE_2; VD, uterine contractions & ↑ platelet aggregation.
- PGD_2; inflammatory response, bronchoconstriction & VD.
- $PGF_{2\alpha}$; VC, bronchoconstriction & uterine contractions.
- TXA_2; ↑ platelet aggregation, VC & bronchoconstriction.
- LTB_4; chemotaxis and T-cell proliferation.
- LTC_4, LTD_4, LTE_4; VC and bronchoconstriction.

Two forms of cyclooxygenase (COX); COX-1 and COX-2.
- COX-1 is *expressed constitutively* in **gastric mucosa, kidney** and **platelets**
- COX-2 is *expressed* in **macrophages** and **monocytes** ***in response*** to **inflammation.**

Aspirin is an ***irreversibly inhibitor*** of **cyclooxygenase (COX)** ***enzyme***, *while* ***other* NSAIDs** are ***reversible*** **inhibitors.**

Selectivity for **COX-1** ***versus*** **COX-2** is ***variable*** and ***incomplete*** for the ***older* NSAIDs**, but ***selective* COX-2 *inhibitors* (*such as* Celecoxib)** *have been* ***synthesized.***

I) Aspirin and other NSAIDs

Acetylsalicylic Acid (Aspirin) (Aspirin®)#

- **Aspirin** is the ***prototype*** of the **NSAIDs**, it is a ***weak* organic acid** that is **unique** (***only***) **NSAIDs** in ***irreversibly inactivating* cyclooxygenase (COX-1** and **COX-2)**, ***other* NSAIDs** (*including other salicylates*), are ***all reversible inhibitors*** of **cyclooxygenase.**

Aspirin is ***now rarely* used** as **anti-inflammatory**, and **used *only*** as **anti-platelet (75-325 mg/d).**

- ***Salicylates*** (*except* **Diflunisal**) ***cross*** *both* **BBB & placenta.**

Mechanism; **Aspirin *irreversibly inhibits* COX**; ***synthesis*** of ***new* COX *replaces*** the ***inactivated* enzyme *lasts* 6-12 hours.**

Antiplatelet effect; **Aspirin *irreversibly inhibits* COX *within*** the **platelets ⇨ *blocks*** the ***formation*** of TXA_2, ***Antiplatelet effect*** of **Aspirin *lasts* 8-10 days** (*the life of the platelet*).

Therapeutic Actions of NSAIDs; 3 *major* therapeutic actions;
1) ***Anti-inflammatory actions***; ***decrease* prostaglandins *synthesis* ⇨ *inhibits* inflammation.**
2) ***Analgesic action***; ***decrease*** PGE_2 **synthesis ⇨ *decrease* pain sensation.**
3) ***Antipyretic action***; ***decrease*** PGE_2 **synthesis ⇨ thermoregulatory center ⇨ ↑ heat loss** *by* ***peripheral* vasodilation** & **sweating** in ***patients with*** **fever.**

GIT; * **Ulceration** and **GI Bleeding** *
- **NSAIDs *inhibit* COX-1 ⇨ *reduce* beneficial *effects* of PGs** in the **GIT.**
- **Patients** with a ***high* risk** for **GI events, NSAIDs *should be* used *concomitantly*** with **proton pump inhibitors** or **Misoprostol** (***PGE_1 analogue***) to ***prevent*** **NSAID-induced ulcers.**
- ***Selective* COX-2 *inhibitors***, have ***less effect*** on **GI ulceration** and **bleeding.**

Platelets; * Antiplatelet Effect *

- Aspirin inhibits the synthesis of TXA_2 by *irreversible acetylation* of COX enzyme.
- *Other* NSAIDs also *inhibit* COX *but* have a *shorter duration* of inhibitory action *because* they *cannot* acetylate COX; that is their action is *reversible*.
- The *recommended dose*; ranges from 75-325 mg/d.
- Aspirin inhibit platelet function *within* 60 min.
- *N.B.*; *Concomitant administration* of *other* NSAIDs can *diminish* the antiplatelet effects of *low-dose* Aspirin, *increase* the risk of thromboembolic effects.
- Aspirin *not given* at *least* 1 week *before* surgery (*Antiplatelet effect of* Aspirin *lasts* 8-10 days).

Kidney; * *Decrease* Renal Blood Flow *

- NSAIDs *inhibit* COX-1 ⇨ *reduce* beneficial PGs in the Kidneys ⇨ *decrease* renal blood flow due to *constriction* of *afferent* arterioles.
- *Selective* COX-2 *inhibitors*, have *less effect* on renal blood flow.

Heart;

- NSAIDs with a *very high degree* of COX-1 *selectivity* (such as Aspirin); have a cardiovascular protective effect, due to *decrease* TXA_2 production *mediated by* COX-1.
- NSAIDs with a *very high degree* of COX-2 *selectivity* (such as Rofecoxib), have a *high risk* for cardiovascular events (MI and stroke), due to *decrease* PGI_2 production *mediated by* COX-2.
- Aspirin in *high dose* (> 325) *inhibit* PGI_2 production *mediated by* COX-2 and may carry a *risk* for CVS events.

Lung; * *Bronchospasm* *

- NSAIDs cause *shift* in arachidonic acid *from* COX pathway *to* LOX pathway ⇨ leukotrienes *formation* ⇨ bronchospasm *may occur* (about 10% of people taking NSAIDs).
- Leukotrienes receptor *antagonists* (Montelukast) are *used* to *overcome* NSAIDs *induced* bronchospasm.

NSAIDs *should be* used at the;
***lowest* effective dose for the *shortest possible* duration of therapy**

Uses of NSAIDs;

A) **Anti-inflammatory** and **analgesic**; such as; **rheumatoid arthritis (RA)**, **osteoarthritis (OA)** & **gout**, **headache**, **toothache**, **backache**, **menstrual cramps (dysmenorrhea)** and **cold/flu**.

B) **Antipyretic**; **Aspirin** is ***contraindicated*** in **children** (*under 20 years*) as **antipyretic *with* viral infections** such as chickenpox or influenza), due to ***increased*** **risk** for **Reye syndrome**.

C) **Antiplatelets**; ***Low-dose* Aspirin *used*** in the ***prophylactic treatment* of transient cerebral ischemia and thromboembolic stroke**, and ***reduce* the incidence of recurrent MI**.

D) **Pregnancy**; ***Low-dose* Aspirin *may be beneficial*** in **pregnancies** at ***risk for*** the ***development*** of **pregnancy-induced hypertension** and **pre-eclampsia**, and in **fetuses with intra-uterine growth retardation**.

D) **Topical**;

1) NSAIDs may be **used topically as anti-inflammatory** and **analgesic**.
2) **Salicylic acid** is a ***keratolytic***, **used *topically*** to ***treat* corns**, **calluses** and **warts**.
3) **Methyl salicylate** is a **counterirritants**, **used *topically* arthritis** and **sports rubs**.

***General* side effects** for ***all* NSAIDs** (*commonly dose related*);
- **CNS**: headaches, tinnitus and dizziness.
- **CVS**: hypertension, fluid retention, edema and risk for CV events.
- **GIT**: abdominal pain, dysplasia, nausea, vomiting, ulcers or bleeding.
- **Kidney**: renal insufficiency, renal failure, hyperkalemia & proteinuria.
- **Lung**: asthma.
- **Hematologic** (*rare*); thrombocytopenia and aplastic anemia.
- **Hepatic**: (*rare*) abnormal liver function tests and liver failure.
- **Skin**: rashes

Reye's syndrome; ***rare serious* condition *characterized by acute* encephalopathy *and* hepatic dysfunction**; **Reye's syndrome *typically affects* children** and **teenagers *after*** a **viral infection** (*flu* or *chickenpox*), and is ***associated with*** the ***use of* Aspirin *during*** the **illness**.

Pregnancy;
- ***Most* NSAIDs** are **category C** in the ***first*** and ***second*** **trimesters**.
- ***All* NSAIDs *should not*** (**category D**) be **used** in **third trimester**, may ***increases*** the **risk** of **pulmonary hypertension** in **newborns**, ***due to premature* closure of the ductus arteriosus** (**NSAIDs *block*** the *synthesis* of **PGE_1** & **PGE_2**, which are ***needed to* keep *open*** the **ductus arteriosus**).

Lactating women;
- ***Most* NSAIDs *displace* bilirubin** and are ***contraindicated*** if a **neonate *with* jaundice**.
- **Ibuprofen**, **Indomethacin** and **Naproxen *safe*** in **breastfeeding women**.

II) Specific Agents

Salicylates

Diflunisal (Dolobid®)

Diflunisal is a **difluorophenyl *analogue*** of **salicylic acid**; ***not cross* BBB**.
- It is ***used*** in **rheumatoid arthritis** (**RA**), **osteoarthritis** (**OA**) and **muscle pain**.
- **Diflunisal** also had the ***advantage*** of a **twice daily *dosage***.
- It ***reported*** causes ***less* GIT ulceration** and **tinnitus** *than* **Aspirin**.
- **Diflunisal oral ointment** is a clinically ***useful* analgesic** for ***painful* oral lesions**.

Propionic Acid Derivatives

Ibuprofen (Advil®)#	**Dexibuprofen** (Extragesic®)	**Ketoprofen** (Ketofan®)#
Dexketoprofen (Dextrafast®)	**Flurbiprofen** (Nalfon®)	**Fenoprofen** (Nalfosab®)
Loxoprofen (Roxogesic®)	**Naproxen** (Aleve®)#	**Oxaprozin** (Daypro)

All of these* drugs *possess* anti-inflammatory, analgesic** and **antipyretic *activity and *may be* **used** in ***chronic treatment*** of **rheumatoid** and **osteoarthritis**; because ***their* GI side effects** are ***generally less* intense *than*** that of **Aspirin**.

Ibuprofen; ***lowest* risk** of causing **GI bleeding** (*this advantage is lost at high doses*). It has ***about* 4 times** the ***analgesic potency*** of **Aspirin**. It is ***available*** in ***multiple* formulations**. **Ibuprofen** and **Indomethacin** are ***effective*** in ***closing* patent ductus arteriosus *in* preterm infants**.

Dexibuprofen is the ***active*** **dextrorotatory** ***enantiomer*** of **Ibuprofen**.

Ketoprofen; ***higher*** **COX-1 selectivity** and **LOX** (*lipoxygenase*), ***less*** **potent** ***than*** **Indomethacin**, ***maximum dose*** is **300 mg/day**.

Dexketoprofen is the ***active*** **dextrorotatory** ***enantiomer*** of **Ketoprofen**.

Flurbiprofen is ***available*** in an ***ophthalmic formulation*** for ***inhibition of*** **intraoperative miosis**, as well as it is also ***orally*** for ***available*** **arthritis**.

Naproxen; It is the ***only*** **NSAID** presently as a ***single*** **enantiomer**, has a ***lowest*** **risk** of **CV events** (*but not without risk*), ***intermediate*** **risk**. It ***may be used alone*** in **menstrual migraine** ***prophylaxis*** or in ***combination*** (**Sumatriptan/Naproxen Treximet®**) in **migraine** ***acute attack***, ***like other*** **NSAIDs** used for ***mild*** to ***moderate*** **pain** & for **rheumatoid**, **osteoarthritis** and **primary dysmenorrhea**. It has been associated with ***pseudoporphyria*** and ***photosensitivity*** in ***some patients***.

Oxaprozin is a ***unique*** *among the* **propionic acid group** of **NSAIDs**, ***because*** it has a ***rapid*** **onset of action** and a ***prolonged*** **duration of action** (half-life 50–60 hours). It also has ***mild*** **uricosuric properties** and is ***more useful*** in **gout** ***than*** some ***other*** **NSAIDs**.

Acetic Acid Derivatives		
Indomethacin (Indocid®)#	**Diclofenac** (Voltaren®)#	**Aceclofenac** (Bristaflam®)#
Ketorolac (Ketolac®)#	**Etodolac** (Etodine®)	**Sulindac** (Clinoril®)
Tolmetin (Rumatol®)		**Nabumetone** (Nabuxan®)

Indomethacin; is a ***very potent*** ***non-selective*** **COX inhibitor** (***one*** **of the** ***most potent*** **NSAIDs**), It is also a ***more*** **potent** ***antipyretic*** than *either* **Aspirin** or **Paracetamol**, and it has ***about*** **10 times** the ***analgesic potency*** of **Aspirin** and about ***6 times*** the ***analgesic potency*** of **Ibuprofen**. **Indomethacin** may also ***inhibit*** **phospholipase A** and **C**, ***reduce*** **neutrophil** ***migration*** and ***decrease*** **T-cell** and **B-cell proliferation**, *so it is* **mainly** ***used for*** **acute gout** *and* **rheumatoid arthritis**. **Indomethacin** are ***effective*** in ***closing*** **patent ductus arteriosus** ***in*** **preterm infants**. It has been ***used for*** ***many*** **other conditions**, ***ophthalmic preparation*** is efficacious for **conjunctival inflammation** and to ***reduce*** **pain** ***after*** **traumatic corneal abrasion**, **Indomethacin** ***oral rinse*** are ***used for*** **gingival inflammation**. **Indomethacin** has ***moderate*** ***high*** **risk** of **CV events**, has a ***very high*** **risk** of **GI complications** and ***many*** **CNS side effects**. [**Indomethacin** **suppositories** ***should be used*** with ***extreme caution*** in **CHILDREN** ***younger than*** **15 year old** (*safety and effectiveness in these children have not been confirmed*).]

Diclofenac is **one** of the ***most potent*** **NSAIDs**, is ***more potent*** **anti-inflammatory** *than* **Indomethacin** and **Naproxen**. **Diclofenac** may also be a ***unique member*** of the **NSAIDs**, it ***inhibits*** the **lipoxygenase pathways** and also may ***inhibit*** **phospholipase A2** with ***higher*** **COX-2 selectivity**, it ***used widely*** in the treatment of **pain** ***associated with*** **renal stone** (*first choice NSAID for renal colic*). It has been ***used for*** ***many*** **other conditions**, ***very high*** **risk** of **CV events** and ***moderate*** **risk** of **GI complications**. [*Don't waste your time to differentiate between diclofenac sodium and potassium*], [**Diclofenac** **suppositories** ***should be used*** with ***caution*** in **CHILDREN** ***younger than*** **3 year old** (*safety & effectiveness in these children have not been confirmed*). **Diclofenac** & **Sulindac** cause ***elevation*** of **liver enzymes**, ***increased*** **risk** of **liver toxicity** *compared with* ***other*** **NSAIDs**.

Aceclofenac is the **glycolic acid ester** of **Diclofenac**. The ***incidence*** of **GI complications** of **Aceclofenac** has been reported to be ***significantly lower than*** that of the ***other*** **NSAIDs**, for instance, **2-folds** ***lesser than*** **Naproxen**, **4-folds** ***lesser than*** **Diclofenac**, and **7-folds** ***lesser than*** **Indomethacin**.

Ketorolac is the ***most*** **potent** and ***most effective*** **NSAID analgesic**, with **efficacy** ***comparable to*** **opioids** (The analgesic effect of 30 mg of **Ketorolac** is similar to 10 mg of **Morphine**), it ***used widely*** in ***short-term treatment*** of ***moderately severe pain*** (*usually after surgery*), due to ***highest incidence*** **of side effects**, **Ketorolac** ***should not use for more than 5 days*** (**oral**, **parenteral** and **intranasal**), the **oral formulation** is ***only*** to be ***used as*** **continuation** to **IV** or **IM therapy**.

Etodolac is a ***potent*** **NSAIDs**, The ***anti-inflammatory*** **potency** of **Etodolac** was found to **lie** ***between*** that of **Sulindac** and **Piroxicam**. **Etodolac** has a ***low incidence*** of **GI complications**.

Sulindac is an ***analog*** of **Indomethacin** (***sulfoxide prodrug***), ***developed as*** a ***less*** **toxic**, with ***similar*** **anti-inflammatory** ***potency***, **Sulindac** is ***unique*** **NSAIDs** in ***lesser*** **inhibiting PGs** ***synthesis*** in the **kidneys** (Kidneys can ***deactivate*** the **active metabolite** of **Sulindac** be ***reoxidize*** the **sulfide** to the ***inactive*** ***sulfoxide prodrug***) So, it may be ***one*** of the ***safest NSAIDs*** drugs for ***treating*** **osteoarthritis** in ***older people***. Like **Diclofenac**, **Sulindac** may cause ***elevation*** of **liver enzymes**.

Tolmetin is a **NSAIDs** with a short half-life (1-2 hours) and ***used in*** **osteoarthritis** and **rheumatoid arthritis** and **juvenile rheumatoid arthritis**, with ***mild*** **GI complications** and ***less*** **tinnitus**.

Nabumetone is a **non-acidic NSAID**, is a ***prodrug*** which ***contains*** the **non-acidic ketone**, which is ***quickly*** **metabolized to** give the **naphthyl-acetic acid derivative** (it was designed to ***decrease*** some of the **GI problems** normally associated with the acidic functionality of these agents), ***long*** **half-life** (*more than 24 hours*), is a ***more potent inhibitor*** of **COX-2**, is ***very similar*** to **other NSAIDs**, with ***less*** **GI complications** and ***less*** **risk** of **CV events** (Effects of **Nabumetone** on blood pressure control in hypertensive patients on ACE inhibitors is also good).

Enolic Acid Derivatives (Oxicams)

Piroxicam (Feldene®)#	**Tenoxicam** (Epicotil®)#	**Lornoxicam** (Xefo®)#
Meloxicam (Mobic®)#		

Piroxicam is an **oxicam** (***nonselective COX inhibitor***), at ***high concentrations*** also ***inhibits*** **polymorphonuclear leukocyte migration**, ***decreases*** **oxygen radical production**, and ***inhibits*** **lymphocyte function**. Its ***long*** **half-life** (*once-daily*), ***very high*** **risk** of **GI complications**.

Tenoxicam is an **oxicam**, there is ***no significant difference*** between **Tenoxicam** and **Piroxicam** (*some studies found* **Tenoxicam** ***more*** **effective** and ***better*** **tolerated** than **Piroxicam**).

Lornoxicam is ***unique*** *among the* **enolic acid derivatives** of **NSAIDs** in that it has a ***rapid onset*** of **action** and a *relatively* ***short*** **half-life** (3-4 hours).

Meloxicam has a ***higher*** **COX-2 selectivity** (it was initially introduced as a selective COX-2 inhibitor), it has a ***fewer*** **risk** of **GI complications** with ***high moderate*** **risk** of **CV events**. It is ***available in*** **7.5mg** and **15mg doses**. ***October, 2015***; FDA approved a ***new formulation*** of **Meloxicam** (Vivlodex®) contains ***microparticles*** of **Meloxicam** (using Solu-Matrix Fine Particle Technology) to ***reduce*** **dose** (5mg and 10mg) and ***decrease*** **toxicity** for the ***treatment of*** **osteoarthritis**.

Droxicam is a ***prodrug*** of **Piroxicam**.

Long-term use of **Oxicams** and **Ketorolac** is ***associated with*** an ***increased*** **risk** of **chronic kidney disease**.

Fenamic Acid Derivatives

Mefenamic Acid (Ponstan®)#	**Meclofenamic Acid** (Meclomen®)
Tolfenamic Acid (Fastgraine®)	

Mefenamic acid is a ***non-selective* COX inhibitors** (**COX-2 >> COX-1**) and also *may* ***act as* prostaglandins receptor *antagonist***, these effects may also be ***responsible for*** its ***effectiveness*** in the ***treatment of* primary dysmenorrhoea**. **Mefenamic acid** is also ***used in* osteoarthritis** and **rheumatoid arthritis**.

- **Meclofenamate** or **Meclofenamic acid** as **Mefenamic acid *used for*** treatment of **dysmenorrhoea**, **osteoarthritis** and **rheumatoid arthritis**.
- **Tolfenamic acid** is ***used to*** treat **migraines** and **severe headaches**, It is available in some countries for humans and for animals.

Other Agents

Nimesulide (Sulide®)#

Nimesulide is a ***sulfonanilide derivatives***, is a ***relatively* COX-2 *selective***, it has ***analgesic***, ***antipyretic*** and **anti-inflammatory effects**. It has ***low incidence*** of **GI complications**.

- It ***primary used*** as ***short term*** in the ***treatment*** of ***acute* pain**, and ***primary* dysmenorrhea**.

Nimesulide *should not* be ***taken*** as **long-term**, (*like* **arthritis**), ***due to*** its ***association with*** an ***increased risk*** of **liver toxicity**.

- ***Due to risk*** of **hepatotoxicity**, **Nimesulide** has been ***withdrawn from* market** in ***several* countries**.

Metamizole (Dipyrone) (Novalgin®)#

Metamizole (**Dipyrone**) is a ***non-opioid analgesic drug***.

Metamizole is an ***ampyrone sulfonate*** (***pyrazolone derivatives***) ***analgesic***, ***antispasmodic*** and ***antipyretic***. ***Like* Paracetamol**, it has ***minimal* anti-inflammatory effects**, this agent is ***still*** incorrectly ***classified as*** a **NSAID**.

It was ***first used*** in1922 (Novalgin®) and for ***many years*** it was available **OTC** in ***most countries***, ***until several* reported cases** of **Agranulocytosis**, *but it is still available OTC in some countries*.

Selective COX-2 Inhibitors (Coxibs)

Celecoxib (Celebrex®)#	**Etoricoxib** (Arcoxia®)#
Rofecoxib (Vioxx®)	**Valdecoxib** (Bextra®)
Parecoxib (Dynastat®)	**Lumiracoxib** (Prexige®)

Celecoxib is a ***reversible selective* COX-2 inhibitor** (about 10–20 times more selective for COX-2 than for COX-1). **Celebrex®** was one of Pfizer's ***best-selling drugs***.

Celecoxib is ***approved for*** the treatment of **rheumatoid arthritis**, **osteoarthritis**, and ***acute mild*** to ***moderate* pain** (has similar efficacy to NSAIDs in the treatment of pain).

Celecoxib is ***associated with less* GI complications *than* other NSAIDs**. ***Like other NSAIDs***, it has a ***similar* risk** of **CV events**, it has a **sulfonamide *structure*** (***contraindicated*** for ***patients*** with **sulfa allergy**). **Celecoxib *metabolism*** is ***primarily by* CYP2C9**, **Fluconazole** and **Fluvastatin**, may ***increase*** serum levels of **Celecoxib**.

Rofecoxib; **Merck & Co.** ***withdrew* Vioxx®** from market **voluntarily**, due to an ***increased* risk** of **CV events**; **heart attack** and **stroke** (**Rofecoxib** inhibits COX-2 80 times more than the COX-1).

- **Valdecoxib**; **Pfizer** ***withdrew*** **Bextra®** from the US market on recommendation **by the FDA** due to an ***increased*** **risk** of **CV events**.
- **Parecoxib** is a ***water-soluble*** and ***injectable*** ***prodrug*** of **Valdecoxib**, It is marketed in the Europe.
- **Etoricoxib** is ***approved in some countries*** *such as* **Egypt** (*not in US*) by **Merck & Co.**
- **Lumiracoxib** is still sold in ***few countries*** by **Novartis**.

NSAIDs *should be* used *at the*;

 # *Lowest effective* dose *for the*
 # *Shortest possible* duration of therapy.

➢ Special Populations:-

Population or Disease State	Preferred Agents
- Pregnancy	- 1st, 2nd trimesters; *Most* NSAIDs are Category C - 3rd trimesters; *All* NSAIDs are Category D
- Patent Ductus Arteriosus (PDA)	- Indomethacin or Ibuprofen.
- Primary Dysmenorrhoea	- Mefenamic acid, Ibuprofen and Naproxen.
- High CV Risk (Coronary Diseases)	- *All* NSAIDs are ***should be avoided***. - *If must be used*, Naproxen appears to be the ***least*** CVS risk.
- High GI Risk (ulcers or bleeding)	- *All* NSAIDs are ***should be avoided***. - *If must be used*, Ibuprofen and Celecoxib appears to be the ***least*** GI risk and used as **co-therapy** with Misoprostol or ***proton pump inhibitors*** (e.g. Omeprazole).
- Asthma and COPD	- NSAIDs can ***prescribed to*** patients with asthma who ***have no previous*** history of NSAID-associated symptoms. - ***About*** 8-20% of adult asthmatics ***experience*** bronchospasm *following ingestion* of NSAIDs. - People who ***have had*** a ***hypersensitivity reaction*** to a NSAID ***should avoid all*** NSAIDs.
- Renal Diseases	- *All* NSAIDs are ***should be avoided*** in ***people*** with Chronic Kidney Disease (CKD). - *If must be used*, Sulindac, Aspirin and Ibuprofen appears to be the ***least*** nephrotoxic risk.
- Renal Stone (Renal Colic)	- Diclofenac (*strongest in effectiveness in renal* colic).
- Children	- Ibuprofen is the ***most appropriate*** NSAID ***for*** children.

- **COX-Inhibiting Nitric Oxide Donators** (**CINODs**); Are a new class of non-steroidal anti-inflammatory drug (NSAID) with a nitric oxide (NO)-donating moiety by improving vascular safety, most likely via vasodilatation such as Naproxcinod (NO-naproxen).

Paracetamol

Paracetamol or Acetaminophen (Panadol®)# (Tylenol®)# (Calpol®)#

- **Acetaminophen** is the name **generally** ***used in*** the **US** and **Japan**, **Paracetamol** is used in ***internationally***.
- ***Both*** *come from* a **chemical name**;
  - Para-**acetyl**a**minophen**ol; **Acetaminophen**.
  - **Para-acetyl**a**minophen**ol; **Paracetamol**.

Tylenol® is an ***American*** **brand** of **Acetaminophen**; ***derived from*** the chemical name; N-ace**tyl**-para-amino**phen**ol (APAP) (or para-acetylaminophenol); **Tylenol®**.

Panadol® is one of GlaxoSmithKline's (GSK) trade names for **Paracetamol**.

Calpol® is a brand of **Paracetamol** children's medicine sold in the UK & other countries

It is ***typically by*** **oral route** ***but*** is ***also available*** **rectally** and **intravenously** (**perfalgan®**).

- **After** ***more than*** **100 years**, the ***exact*** ***mechanism*** of **Paracetamol** is ***still*** **unclear**.

Paracetamol is an **analgesic/antipyretic** ***of choice*** for;

- **Children**, with **viral infections** or **chickenpox**; Due to the risk of Reye syndrome with aspirin.
- **Pregnancy** and **breastfeeding women**.
- ***Patients with*** **CV risk** or **GI complications**.
- **Asthmatic patients**.

Therapeutic Uses;

- **Fever**, **Pain** (***mild*** *to* ***moderate pain***).
- **Headaches**; **Paracetamol** in ***combination with*** **Caffeine** is ***highly effective*** in treatment of **tension** or **migraine headache**.
  - **Caffeine** ***accelerates*** **absorption** & ***enhances*** the **analgesic effect** of **Paracetamol**
- **Osteoarthritis**; In 2012 the American College of Rheumatology ***recommends*** **Paracetamol** with ***other*** **several options** for ***people with*** **osteoarthritis**.

Panadol® Family

- **Panadol Blue** (**Paracetamol** 500mg); regular tablets.
- **Panadol Extra** (**Paracetamol** 500mg + **Caffeine** 65mg); regular tablets.
- **Panadol Actifast** (**Paracetamol** 500mg + **Sodium** 173mg); absorbed twice as fast as regular paracetamol.
- **Panadol Advance** (**Paracetamol** 500mg); Optizorb Technology absorbs 5 times as fast as regular paracetamol.
- **Panadol Joint** (**Paracetamol** 665mg); 2 tablets taken three times a day.
- **Panadol Night** (**Paracetamol** 500mg + **Diphenhydramine** 25mg); 2 tablets 30 minutes before bed.
- **Panadol Cold + Flu Day** (**Paracetamol** 500 mg + **Caffeine** 25 mg + **Phenylephrine** 5mg)
- **Panadol Cold + Flu** (**Paracetamol** 500 mg + **Chlorpheniramine** 2 mg + **Pseudoephedrine** 30 mg).
- **Panadol Cold + Flu All in one** (**Paracetamol** 250 mg + **Guaifenesin** 100 mg + **Phenylephrine** 5 mg).

- **Panadol Cold + Flu Hot lemon and Honey sachet** (**Paracetamol** 600 mg + **Vitamin C** 40 mg + **Phenylephrine** 10 mg).
- **Panadol Sinus** (**Paracetamol** 500 mg + **Pseudoephedrine** 30 mg).
- **Panadol Migraine** (**Paracetamol** 250mg + **Acetylsalicylic acid** 250mg + **Caffeine** 65mg); 2 tablets every 6-8 hours.
- **Panadol Baby & Infant Suspension** (**Paracetamol** 120mg/5ml); 3 months to 5 years.
- **Children's Panadol elixir** (**Paracetamol** 240mg/5ml); 5-12 years.

Dose;

- *Medicines and Healthcare products Regulatory Agency (MHRA) guidelines for* **IV** ***Paracetamol*** *dosing (most accurate and updated);*

Weighing	Dose per administration	Max. daily dose
< 10 kg	7.5 mg/kg	30 mg/kg
10-33 kg	15 mg/kg	60 mg/kg (max. 2gm)
33-50 kg	15 mg/kg	60 mg/kg (max. 3gm)
>50 kg	1 gm	4 gm

 # N.B.; - ***Maximum single adult dose***: **1 gm** (oral or IV).
- ***Minimum dosing interval***: ***every* 4 hours**.
- ***Acute ingestion*** of **15 g** of **Paracetamol** ***may be* fatal**, **death** being ***caused by severe* hepatotoxicity**, *sometimes associated with* **acute renal tubular necrosis**.

Toxic Dose; ***Acute ingestion***; > 150-200 mg/kg in children or 7 g in adult is considered potentially toxic.

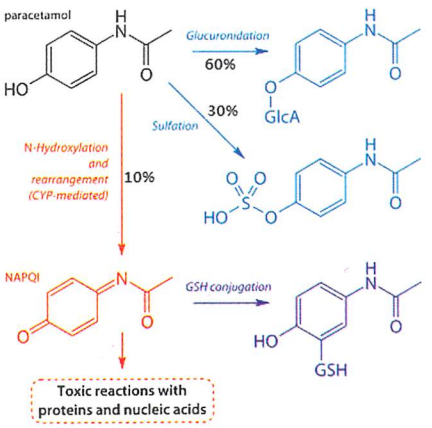
- ***Severe renal impairment*** (CrCl less than 30 mL/min); ***Longer* dosing intervals** and a ***reduced* total daily dose**.
- ***Severe hepatic impairment***; **Paracetamol** is ***contraindicated***.

Mild to ***moderate* hepatic impairment**: ***Used with* caution** (***reduce* total daily dose** and/or ***used in combination with* glutathione analogues** such as; **Methionine** (is an essential amino acid which serves as a precursor for the amino acid **Cysteine** which will be incorporated in glutathione "GSH" synthesis.

At normal therapeutic doses, **Paracetamol** is ***virtually free*** of ***significant* side effects**. ***With large doses***; **Hepatic necrosis** (a ***very serious*** and ***potentially* life-threatening condition**) ***may occur***.

☞ ***Metabolism in therapeutic dose***;

- *About 60%* of **Paracetamol** by **glucuronidation** and ***about 30%*** by **sulfonation** ⇨ to ***inactive* products**.
- *About 10%* by **cytochrome P450** (CYP3A4 and CYP2E1) ⇨ to **alkylating metabolite** ***known as* NAPQI** (N-acetyl-p-benzoquinone imine) ⇨ ***Highly toxic but rabidly* detoxified** by ***irreversibly conjugated*** with the **sulfhydryl groups** of **glutathione**.



☞ ***Metabolism in toxic dose***;

- ***High dose*** of **Paracetamol** cause ⇨ ***saturation*** of **glucuronidation** ⇨ ***shunting metabolism*** to **cytochrome** ⇨ ***increase amount*** of **NAPQI** ⇨ **glutathione system** ***not able*** to **detoxify NAPQI** ***due to depletion*** of **–SH group** ⇨ **Acute hepatic necrosis**.

- ***Clinical manifestation during toxicity***;
  - **Phase I** (during 24 hours);
    - **Nausea**, **vomiting** and ***may be*** **asymptomatic**.
    - ***Normal*** **hepatic transaminases ALT** and **AST**.
    - ***Normal*** **hepatic transaminases ALT** and **AST**.
  - **Phase II** (24-72 hours after ingestion);
    - Signs of ***liver damage*** are ***increased*** e.g. **right upper quadrant pain** and ***mild*** **increase** in **ALT** and **AST**.
  - **Phase III** (3-4 days after ingestion);
    - ***Symptoms of*** **hepatic necrosis**; **hepatic encephalopathy**, **jaundice**, **coagulopathy** and **hypoglycemia**.
    - **Acute renal failure** ***may*** **develops**.
    - **Death** ***may occur*** from **multiorgan** ***failure***.
  - **Phase IV** (3-4 weeks) (**recovery phase**):
    - **Clinical recovery** may take up to **21 days**; however, ***complete*** **hepatic histologic** ***recovery*** requires ***several*** **months**.

Antidote;

- ***N***-acetylcysteine (NAC) is ***nearly*** **100%** **hepatoprotective** ***within*** **8 h.** ***after*** an ***acute*** Paracetamol ingestion;
  - Oral NAC; ***loading dose*** of 140 mg/kg, ***followed by*** 70 mg/kg, every 4 hours for 17 doses.
  - IV NAC; - ***loading dose***: 150 mg/kg IV in 200 mL of 5% dextrose and infuse over 1 h.
    - ***Dose 2***: 50 mg/kg IV in 500 mL 5% dextrose over 4 h.
    - ***Dose 3***: 100 mg/kg IV in 1000 mL 5% dextrose over 16 h.

Opioid Analgesics

- **Opioids**; are **natural**, **semisynthetic**, or **synthetic compounds** that **produce morphine-like effects**.
All opioids act by binding to specific **opioid receptors** to **produce effects** that mimic the action of **endogenous opioid peptide neurotransmitter** (**Endorphins**, **Dynorphins** and **Enkephalins**).
- **Opium**; is the **dried latex obtained from** the **opium poppy** (***Papaver somniferum***).
- **Opium latex**; contains **Morphine**, may used chemically to produce **Heroin** and **other opioids**.
- **The term "opioid"** originated in the 1950s. It combines **"opium"** + **"-oid"** meaning **"opiate-like"** ("opiates" being morphine and similar drugs).
- **Narcotic**; derived from words meaning **numbness** or **sleep**, is **now** a **legal term** that **refers to opioids**.

Morphine

Morphine (MS Contin®)#

- **Morphine** (***prototype***) is a **phenanthrene** (*chemical class*) ***strong* μ receptor *agonist***.
* **Clinical Use of Opioid** (**Morphine** and ***other opioids***) **Analgesics** *
  1) **Analgesia** (***relief* pain *without* loss of consciousness**).
  2) **Acute Pulmonary Edema**.
  3) **Cough Suppression**.
  4) **Diarrhea**.
  5) **Preanesthetic Medication**.
Side effects; **Tolerance**, **dependence** and **acute side effects** (**Respiratory depression**, **nausea**, **vomiting**, **allergic reactions**, **bronchoconstriction** and **constipation**).

Specific Agents

Strong Agonists

Phenanthrenes

Hydromorphone (Dilaudid®)#

Hydromorphone is a ***semi-synthetic* Morphine *derivative***, is ***hydrophilic like***, ***more* water soluble**.
Oral* Hydromorphone** (*usual oral dose* 1.5 mg) is *approximately* **8-10 times *more potent than **Morphine** (*usual oral dose* 10 mg).
Extended-release (*once-daily*) **formulation** of **Hydromorphone** (**Exalgo®**) is *available*.
- **Morphine** are ***contraindicated*** in **renal failure**, while **Hydromorphone** is **used *with caution***.

Oxymorphone (Opana®)#

- **Oxymorphone** is a ***semi-synthetic* Morphine *derivative***, is ***more* lipid *soluble*** than **Morphine**, resulting in a ***rapid onset of action*** when given in **oral route**.
- **Oxymorphone**, ***Parenterally***; *approximately* **10 times *more potent*** than **Morphine**.
  Orally; *approximately* **3 times *more potent*** than **Morphine**.
Extended-release (*once-daily*) **formulation** of **Oxymorphone** (**Opana® ER**) is *available*.

Methadone (Dolophine®)#

- **Methadone** is a ***synthetic*** **opioids, structurally *unrelated*** to **Morphine**.
- ***Uses***; - **Pain (neuropathic pain** is ***included*** due to ***non*-opioid mechanisms)**.
  - **Control withdrawal symptoms** of **opioid dependency** (**Methadone Maintenance Treatment**; **MMT**), induced ***less*** **euphoria, tolerance** & **physical dependence** develop ***more slowly*** & **withdrawal symptoms** are ***milder*** than **Morphine**.
- ***N.B.***; - **Methadone** can ***prolong*** the **QT interval.**

Meperidine or Pethidine (Demerol®)#

- **Meperidine** or **Pethidine** is a ***synthetic*** **opioid, structurally *unrelated*** to **Morphine**, but ***related*** to **Atropine**, it is ***very*** **lipophilic** and has ***anticholinergic effects***, ***increased*** **incidence** of **delirium**.
- It is ***metabolized to*** an **active metabolite Normeperidine** (***neurotoxic*** and ***serotonergic effects***).
- It is a **κ *agonist*** and also has **local anesthetic *effects***.

It is the ***preferred*** **opioid** in *some countries* ***used*** in **labour** and **delivery**.

- *Due to* **anticholinergic effects**, It is preferred in **pain *associated with* biliary spasm** or **renal colic**.
- **Serotonin syndrome** has also been ***reported*** in patients receiving both **Meperidine** and **SSRIs**.

Fentanyl (Duragesic®)#

Fentanyl is **one** of the ***most widely synthetic opioids* used**.

- It is *approximately* **80-100 times *more* potent *than* Morphine** and *approximately* **40-50 times *more* potent *than* Heroin**, it is ***highly*** **lipophilic** and has a ***rapid*** **onset** and ***short*** **duration** of **action**.

Common Routes *and* ***Formulations***;

- ***IV injection***; ***duration***; 30-60 minutes, ***used for* adjunct *to an* anaesthetic** (**analgesic** and **sedative effects**) and **analgesia** for ***moderate*** and ***severe*** **pain**.
- ***Transdermal patch***; ***duration***; 72 hours, ***used for* chronic pain**.
- ***Transmucosal***; **Fentanyl lozenges (Actiq®)**, ***duration***; 1-2 h, ***used in* breakthrough pain** (*sudden flare of pain*), e.g. **breakthrough cancer pain (BTCP)**, **nasal spray**, **sublingual spray**, **sublingual tablets** and **buccal tablets** are **transmucosal *drug delivery*** and are also ***available*** and ***used*** in **breakthrough pain**.

- **Fentanyl** may **produce *more prolonged*** **respiratory depression** than other opioid analgesics, (*especially* **Fentanyl skin patches**).
- **Fentanyl** is ***metabolized to*** **inactive metabolites** by the **CYP3A4, CYP3A4 *inhibitors*** can ***potentiate*** **Fentanyl effects**. ***Inactive*** **metabolites** are ***eliminated*** **renally**.
- **Fentanyl** appears to be ***safe*** to ***use in*** **renal failure.**

Alfentanil (Alfenta®) | Sufentanil (Sufenta®) | Remifentanil (Ultiva®)

- **Sufentanil**, a ***potent analgesic*** (5-10 times more potent than **Fentanyl**).
- **These agents** are ***mainly*** **used** for **adjunct *to an* anaesthetic** (analgesic and sedative effects) ***during* surgical procedures**. **Sufentanil** appears to be ***safe*** to ***use in*** **renal failure**.

Mild to Moderate Agonists

Codeine

Codeine (**3-Methyl-Morphine**) is a ***natural*** **opioid alkaloid** (2% of opium) and is a ***weak agonist***. **Codeine** is ***converted to*** **Morphine** by **CYP2D6 enzyme** in the liver.
It is *typically* ***used*** to ***treat*** ***mild*** to ***moderate*** **pain**, and ***commonly*** used in ***combination with*** **Paracetamol** (**Tylenol® No.3**) or **Aspirin** (**Co-codaprin®**).
Codeine exhibits ***good antitussive activity*** at **doses** that ***do not cause*** **analgesia**.

Hydrocodone (Lortab®) | Oxycodone (Oxycontin®)

- **Hydrocodone** and **Oxycodone** are ***semi-synthetic*** **Codeine** ***derivative***. **Hydrocodone** is ***stronger than*** **Codeine** (about 50%), while **Oxycodone** is ***stronger than*** **Hydrocodone** (about 50%).
- **Hydrocodone** & **Oxycodone** are used to treat ***moderate*** to ***severe*** **pain**, and ***sometimes*** used in ***combination with*** **NSAIDs**. ***Extended release*** **formulations** are available.

Partial Agonists and Mixed Agonist-Antagonist

Buprenorphine (Subutex®)#

- **Buprenorphine** is a ***partial agonist***, at **μ receptor**, and ***antagonist*** at **κ** & **δ**.
It **cause** ***mild*** **withdrawal symptoms** and ***little*** **sedation**, **respiratory depression** or **hypotension** ***even at*** **high doses** (*advantage over* **Methadone**), so it is ***widely used*** to ***treat*** **opioid addiction** (**opioid detoxification**) or **opioid dependence**, and may ***use*** to treat ***moderate*** to ***severe*** **pain**,
Routes of administration; **Injection** and **transdermal patch** are ***indicated for*** **pain**, while **sublingual tablet** is ***indicated for*** **opioid dependence**.
Buprenorphine also **available** in a ***combination with*** **Naloxone** (***opioid antagonist***) (**Suboxone®**) at a 4:1 ratio, **sublingual tablet** is ***used*** for **opioid dependence** (*see withdrawal symptoms*).

Nalbuphine (Nubain®)#

- **Nalbuphine** is a ***mixed agonist-antagonist***.
It is ***used*** **parenterally** ***for***; ***moderate*** to ***severe*** **pain**, ***supplement*** to **balanced anesthesia** (preoperative and postoperative analgesia) and **obstetrical analgesia**.

Butorphanol (Stadol®)#

- **Butorphanol** is a ***mixed agonist-antagonist***.
- It ***produces*** **analgesia** ***equivalent to*** **Nalbuphine** & **Buprenorphine** ***but*** it ***produce more*** **sedation**.
Butorphanol **intranasal spray** is ***indicated for*** **migraine**, **Butorphanol** **injection** is ***indicated for*** ***moderate*** to ***severe*** **pain**, ***supplement*** to **balanced anesthesia** and **obstetrical analgesia**.

Pentazocine (Talwin®)#

- **Pentazocine** is a ***mixed agonist-antagonist***, **κ receptor** ***agonist*** & ***weak*** **μ receptor** ***antagonist***.
Pentazocine **injection or oral** ***alone*** (**Talwin®**) or **oral** ***combination with*** **Naloxone** (**Talwin® NX**) (**Naloxone** not absorbed orally *but* used to prevent drug abuse if injected), is ***indicated for*** ***moderate-severe*** **pain**, ***supplement*** to **balanced anesthesia** & **obstetrical analgesia**.
- ***High*** **doses** ***increase*** **blood pressure** and can cause **hallucinations** (**psychotomimetic** ***effects***; due to its ***action*** at the **κ receptors**).
- **Pentazocine** **should** be ***used with*** **caution** in ***patients with*** **coronary artery disease**.

Other Opioid Analgesics

Tramadol (Contramal®)#

- **Tramadol** is a **μ receptor** ***agonist*** and **norepinephrine/serotonin reuptake** ***inhibitor***.
- It is ***metabolized by*** **CYP2D6, CYP3A4** and **CYP2B6**, ***leading to*** an **active metabolites** with a ***much higher*** **affinity** for the **μ receptor** than **Tramadol**, **metabolites** are ***eliminated*** *primarily* by the kidneys (**dose** ***reduction*** in **renal** and **hepatic** ***impairment***).

It is ***used for*** ***moderate*** to ***moderately severe*** **pain**, for ***severe pain*** it is ***less*** **effective** than **Morphine**.

- Its **respiratory depressant** ***activity*** and **constipation** is ***less than*** that of **Morphine**.

Toxicity of **Tramadol** are ***associated with*** **seizures** (***contraindicated*** in **patients with a history** of **epilepsy** and for use with ***other*** **drugs** that ***lower*** the **seizure threshold**).

Risk of ***serotonin syndrome***, are ***increased*** *especially* if **selective serotonin reuptake inhibitor (SSRI) antidepressants** are ***co-administration*** with **Tramadol**.

Tramadol has been ***associated with*** ***misuse*** (***delay*** **ejaculation** and **wakefulness**) and ***abuse***.

Long*-term use** of ***high **doses** of **Tramadol** will ***cause*** ***dependence*** and a ***withdrawal syndrome***.

- **Tramadol** and ***active*** **metabolites** may be ***detected*** in the **blood** to ***monitor for*** **abuse**.
- ***Fatalities*** with **Tramadol** ***overdose*** *have been* **reported**.

In 2014, **Tramadol** has been ***placed into*** **Schedule IV**.

Tapentadol (Nucynta®)#

- **Tapentadol** is a ***newer*** **analgesic** was ***approved by*** **FDA** in **2008**.
- ***Mechanism of action***; ***modest*** **μ receptor** ***agonist***, ***significant*** **norepinephrine reuptake** ***inhibitor*** (NRI), and ***weak*** **effects** on **serotonin reuptake**. ***Metabolism***; **Tapentadol metabolites** are ***inactive***.

It is ***used for*** ***moderate*** to ***severe*** **pain**, it is also ***indicated for*** **diabetic neuropathy pain** (NRI).

#**Tapentadol** carries ***risk for*** ***seizures*** and for the ***development of*** ***serotonin syndrome***.

- ***In 2015***, **Nucynta®** ***annual sales*** are $166 million.
- **Tapentadol** ***not*** be **placed** ***under*** **international control** ***but*** **remain** ***under*** **surveillance**.

Black box warning; ***May cause serious***, ***life-threatening*** **respiratory depression** and ***risk for*** **addiction, abuse** or **misuse**.

Other Opioids Not Used as Analgesics

Dextromethorphan

- **Dextromethorphan** (**DXM** or **DM**) is the ***dextrorotatory*** of **Levomethorphan**, which is the ***methyl ether*** of **Levorphanol**, ***both*** **opioid analgesics**.
- It is ***free*** of **addictive properties** and produces ***less*** **constipation** than **Codeine**.
- It is ***one*** of the **active ingredients** in ***many*** **over-the-counter (OTC) cold** and **cough medicines**.

The ***primary use*** of **Dextromethorphan** is as a **cough suppressant** (***antitussive***).

Usual antitussive dose is **15-30 mg 3** or **4 times** ***daily***.

At ***high*** **doses Dextromethorphan** acts as an **NMDA receptor** ***antagonist*** (**Hallucinations**).

- It is ***should not*** be taken with **MAO inhibitors** due to the ***potential for*** **serotonin syndrome**.

Diphenoxylate

- **Diphenoxylate**, is an **opioid drug** act as ***antiperistaltic drug*** (***Antimotility Agent***).

Diphenoxylate + **Atropine** (**lomotil**®) ***combination used*** to treat ***severe*** **diarrhea**.

Loperamide (Imodium®)#

Loperamide, is an **OTC opioid drug** act as ***antimotility Agent***.

- **Loperamide** is a **μ receptor** ***agonist*** on the **large intestine**.

Loperamide ***does not cross*** the **BBB**, ***concurrent*** **administration** of **P-glycoprotein** ***inhibitors*** (*mechanism prevents* **Loperamide** *from crossing the BBB*) such as **Quinidine** allow **Loperamide** to cross the BBB, and may produce **respiratory depression**.

- **Loperamide** is effective for the ***treatment*** of a ***many types*** of **diarrhea** (acute nonspecific diarrhea, traveler's diarrhea, irritable bowel syndrome and chronic diarrhea in inflammatory bowel disease).

Drug avoided in ***high*** **fever** and if **stool** is ***bloody*** or ***black***.

It *may* ***increase*** **risk** of **toxic megacolon** (*acute colonic distension*) and **paralytic ileus**.

Opioid Antagonists

Naloxone (Narcan®)#

Naloxone is a ***pure opioid antagonist***, it is used to ***reverse*** the **coma** and **respiratory depression** of **opioid overdose**.

- ***Onset***; ***Within*** **30 seconds** of **IV injection** of **Naloxone**, the **respiratory depression** and **coma** of **morphine** **high doses** are ***reversed***.
- ***Half-life***; **30-81 minutes**, ***shorter than*** the **half-life** of ***some*** **opiates**, ***repeat*** **dosing** ***may require***.
- It is *primarily* ***metabolized*** by the **liver** and ***excreted*** in the **urine**.
- ***In 2014***, the **US FDA** ***approved*** **Evzio**®, a **hand-held automatic injector** **Naloxone**, can be used in non-medical settings such as in the home.
- ***In 2015***, the **US FDA** ***approved intranasal*** **spray** **Naloxone**, ***easy-to-use*** to ***treat*** **opioid overdose**.
- The ***major*** ***uses*** of **Naloxone** is in the ***treatment*** of **acute opioid overdose**.
- It may be ***useful*** as an ***adjunctive agent*** in the ***management*** of **septic shock**.

N.B.; **Naloxone** ***cannot be*** **absorbed** ***orally***, so it is *commonly* ***combined*** with a number of oral opioids, including **Buprenorphine** (**Suboxone**®) and **Pentazocine** (**Talwin NX**®), ***so*** that when **taken orally** just the **opioid** has an **effect**; ***but*** if ***misused*** by **injecting**, the **Naloxone** ***blocks*** the **effect** of the **opioid**.

Naltrexone (Anarcol®)#

- **Naltrexone** has **actions** ***similar to*** those of **Naloxone**.

It is ***orally active*** and has a ***longer duration*** **of action** than **Naloxone** (***single*** **oral dose** of **Naltrexone** ***blocks*** the ***effect*** of ***injected*** **Heroin** for ***up to*** **24 hours**).

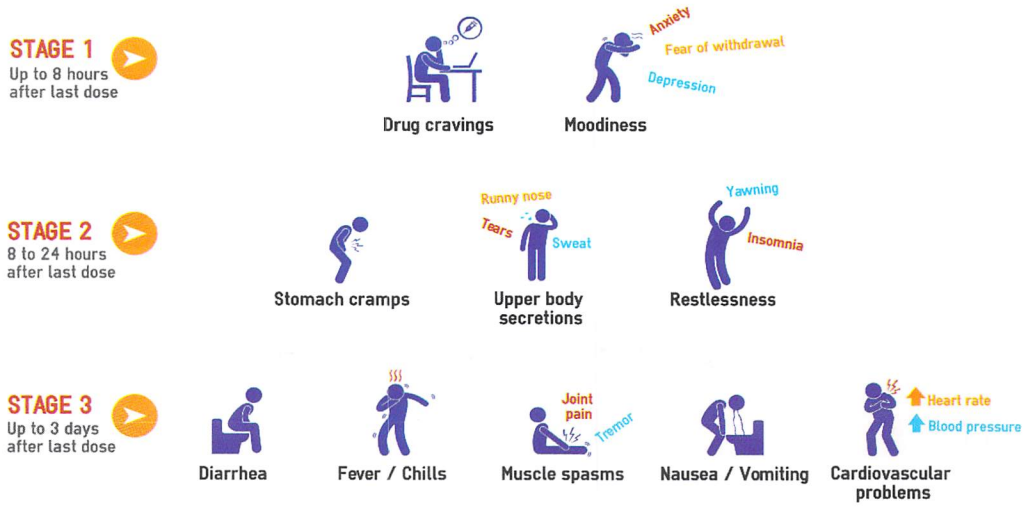
It is ***used*** ***primarily*** in the ***management*** of **alcohol dependence** (**alcoholism**, *unknown mechanism*) and **opioid dependence**. **Naltrexone** in ***combination with*** **Clonidine** (and sometimes with **Buprenorphine**) is ***used for*** **rapid opioid detoxification**.

- **Naltrexone** has been reported to cause **hepatotoxicity** (*dose-dependent*).

Nalmefene (Revex®)#

- **Nalmefene**, is a ***derivative*** of **Naltrexone** (***similar*** in both **structure** and **activity**) ***but*** is **available *only*** for **IV *administration***, ***but*** has a ***longer*** **half-life**, and ***no*** **dose-dependent liver toxicity**.
- It is ***used*** in the ***management*** of **alcohol dependence** and **opioid dependence**.

Heroin Withdrawal Timeline #



Opioid Detoxification

1) Methadone Maintenance Treatment (MMT)

Methadone maintenance has been ***used*** to ***treat*** **opioid dependence** for ***more than* 45 years ago**.

- ***Long-term*** use of **Methadone** as a ***substitute*** (***drug replacement therapy***) to the **opioid** on which the **patient** was ***dependent***.
- ***Dose*** of **Methadone** in **maintenance treatment** *range from* **80-120** mg orally per day.

2) Buprenorphine Maintenance Treatment (BMT)

Some formulations of **Buprenorphine** (**Suboxone®** - **Zubsolv®**) are ***combined with*** the **opiate antagonist Naloxone** to ***protect*** the **pill**; ***prevent*** **people** from ***crushing*** the **sublingual tablets** and **injecting *them***.

- May 26, 2016, ***FDA approve*** **Probuphine®** **implant** to releases a steady six-month dose of **Buprenorphine**.

3) Levacetylmethadol or Levo-α-acetylmethadol (LAAM) (OrLAAM®)

LAAM is a ***long-acting*** (thrice-weekly dosing) **derivative** of **Methadone**, is a ***second-line*** **treatment**, if patients ***fail*** to **respond** to **Methadone** or **Buprenorphine**.

- It may cause ***life-threatening*** **QT interval prolongation**.

4) Opioid Antagonist

- **Naltrexone** (***monthly injection***) ***for*** **relapse prevention** of **alcohol** and **opioid**.

5) α_2-adrenergic Agonist

- **Clonidine** and **Lofexidine** are used to ***control*** **sympathetic symptoms**.

 # # N.B.; **Tropicamide** (***antimuscarinic***) containing **eye drops**, ***used to*** produce ***short-acting*** **mydriasis** and **cycloplegia** is ***currently*** **abused**, as an ***inexpensive*** **euphoric deliriant drug**. It is usually ***mixed*** with **Heroin** and ***other*** **opioids** to ***increase*** the **efficacy** and ***decreasing*** or ***delaying*** the **withdrawal symptoms**.

Skeletal Muscle Relaxants

Muscle relaxants are **two major groups**, **Neuromuscular Blockers** and **Spasmolytics**;

Neuromuscular blockers (**NMBs**) act by **blocking nicotinic acetylcholine receptors** at the **neuromuscular junction** and have **no CNS activity**, they are often **used during surgical procedures** and in **intensive care**.

Spasmolytics; are **centrally acting muscle relaxants**, are **used** to **relief spasms** (***musculoskeletal pain***) and **spasticity** (*neurological conditions*).

Muscle Spasticity; **Muscle tone caused by brain** or **spinal problems**, **such as cerebral palsy** and **multiple sclerosis**. **Treated by**; **Antispastic drugs**, **Baclofen**, **Tizanidine** (first line) and **Dantrolene** and **Diazepam** (***second line***), **Botulinum toxin** (**Botox®**) have been shown to be **effective**.

Muscle Spasms; **Muscle tone caused by musculoskeletal conditions**, **such as back** and **neck pain** and **fibromyalgia**. **Treated by**; **Antispasmodic drugs** **such as** **Cyclobenzaprine** and **Orphenadrine**.

A) Centrally Acting Skeletal Muscle Relaxants

Centrally Antispasticity Agents

Diazepam (Valium®)#

- **Diazepam** ***facilitate*** the **action** of **GABA** in the **CNS** (*both* **brain** and **spinal cord**).
- **Diazepam** has been ***effective*** for **short-term use**; **tolerance** and **addiction** ***can occur***.
- ***Dose***; usual adult dose of **Diazepam** for **muscle spasms*** and **muscle spasticity*** (**antispasmodic** and **antispasticity agent**); 2-10 mg orally 3-4 times daily, OR 5-10 mg IV/IM initially.
- ***Other*** **benzodiazepines** *may* be **used** as **spasmolytics**, ***but*** **clinical experience** with them is ***limited***.

Baclofen (Lioresal®)#

- **Baclofen** is a ***derivative*** of **GABA** (***chlorophenyl*-GABA**) **antispasticity agent**, was ***designed*** to be an **orally active GABA-*potentiating agent***.
- **Baclofen** is an ***agonist*** at **$GABA_B$ receptors**, ***hyperpolarization*** ($\uparrow K^+$) ⇨ ***presynaptic*** **↓ calcium influx** and **↓** ***release*** of **excitatory transmitters** in CNS (*both* **brain** and **spinal cord**) ⇨ **↓ muscle tone** *as well as* **pain** *associated with* **spasticity**.
- ***Uses***; It is ***primarily*** **used** for the ***treatment*** of **muscle spasticity***, ***especially*** in instances of **spinal cord injury** (**SCI**), **cerebral palsy** and **multiple sclerosis** (**MS**).
- ***Dose***; 5 mg 3 times daily for 3 days ⇨ 10 mg 3 times daily for 3 days ⇨ 15 mg 3 times daily for 3 days ⇨ 20 mg 3 times daily for 3 days (Max, 80 mg daily).
- ***Side effects***; **confusion**, **headache**, **insomnia**, **nausea**, **constipation** & ***increase*** **urinary frequency**.
- ***Warning***; ***Abrupt*** **discontinuation** of **Baclofen** can be ***associated with*** a **withdrawal syndrome**; **hallucinations** and **seizures**.

Tizanidine (Sirdalud®)#

Tizanidine is a ***centrally acting*** **α_2 adrenergic agonist** (as **Clonidine**), is an **antispasticity agent**.

- **Tizanidine** ***reduce*** **spasticity** at ***doses*** that *cause* ***fewer*** **cardiovascular effects** ***than*** **Clonidine**.

Uses; *Like* **Baclofen** it is ***primarily*** **used** for the ***treatment*** of **muscle spasticity*** (***some*** **physicians** ***used*** **Tizanidine** in **muscle spasms**).

- ***Dose***; ***Initial***; 2mg orally 3-4 times daily, ***maintenance***; 8mg orally 3-4 times daily, ***max***.; 36mg/day.
- ***Side effects***; **hypotension**, **sedation** and **dry mouth** (*dose-related*).
- ***Warning***; **Hepatotoxicity** (*monitor liver function tests*) and **abrupt discontinuation** can be associated with **rebound hypertension**.
- ***Drug interactions***; **CYP1A2 inhibitors**, *such as* **Ciprofloxacin** and **Fluvoxamine**.

Centrally Antispasmodic Agents

Orphenadrine (Norflex®)#

- **Orphenadrine** is an ***anticholinergic drug*** *closely related to* **Diphenhydramine**.
- **Orphenadrine** is the ***first*** **agent** used in the ***treatment*** of **Parkinson's disease** in **1940s**.
- ***Uses***; as an ***adjunct*** to **rest**, **physical therapy** and ***other*** **measures** for the ***relief*** **muscle spasms*** *associated with* ***acute painful*** **musculoskeletal conditions**.

Orphenadrine also ***combine*** with analgesics; **NSAIDs** (**Aspirin** + **Caffeine**; **Norgesic Forte®**) or with **Paracetamol** (**Norgesic®**).

- ***Common Side effects***; **Confusion**, **constipation**, and **urinary retention** (*Anticholinergic effects*).

Cyclobenzaprine (Flexeril®) (Multi-Relax®)#

- **Cyclobenzaprine** is ***structurally related*** to **tricyclic antidepressants**.
- ***Uses***; It is ***approved*** for **muscle spasms*** *associated with* ***acute*** **musculoskeletal conditions**, It is often used ***off-label*** for **fibromyalgia**.
- ***Dose***; ***Initial***; 5 mg orally 3 times a day (***max***.; 10 mg orally 3 times a day).
- ***Side effects***; **Drowsiness**, **dry mouth** (*Anticholinergic effects*), **fatigue** and **headache**.
- ***Precautions***; ***Use in*** the **elderly** and **patients** *with* **hepatic dysfunction**.
- ***Drug interactions***; **MAO inhibitors** (or *within* **14 days** *after discontinuation*).
- ***Risk***; **serotonin syndrome**.

Carisoprodol (Soma®) (Myorelax®)#

- **Carisoprodol** is a ***carbamate derivative***.
- ***Uses***; **Muscle spasms*** *associated with* ***acute painful*** **musculoskeletal conditions**.
- ***Metabolism***; Extensively metabolized by **CYP2C19**, one of its metabolites, **Meprobamate**, is an ***anxiolytic agent*** (**Meprobamate** is a drug of **abuse** and **dependence**)
- ***Effects***; **analgesia**, **anxiolytic**, **muscle relaxation**, **sedation** and **somnolence**.
- ***Dose***; 250-350 mg orally 3 times a daily.
- ***Side effects***; **Drowsiness** and **dizziness** (*CNS depression*).
- ***Precautions***; ***Use*** **patients** *with* **renal** or **hepatic dysfunction**.
- ***Warning***; **Abuse**, **dependence** and **withdrawal**.

Methocarbamol (Robaxin®) (Ibuflex®)# (Dimra®)# (Methorelax®)#

- **Methocarbamol** is a ***carbamate derivative*** of **Guaifenesin** (*expectorant*).
- ***Uses***; as an ***adjunct*** to **rest, physical therapy** and ***other*** **measures** for the ***relief*** **muscle spasms*** *associated with* ***acute painful*** **musculoskeletal conditions, and *control*** of **neuromuscular manifestations** of **tetanus**.

Methocarbamol also ***combine*** with analgesics; **NSAIDs (Ibuprofen; Ibuflex®, Diclofenac Potassium; Dimra®)** or with **Paracetamol (Methorelax®)**.

- ***Metabolism***; by **dealkylation** and **hydroxylation** and **conjugation** (*unlike* **Carisoprodol, Methocarbamol metabolites *not*** has **greatly abuse potential**).
- ***Formulations***; **oral** and **parenteral**.
- ***Dose***; ***Initial***; 1500 mg orally 4 times daily for the first 2 to 3 days, ***followed by*** 750 mg orally 4 times daily.
- ***Side effects***; **lightheadedness, dizziness** and **drowsiness**.
- ***N.B.***; **black, brown** or **green urine** are ***possible***.

Metaxalone (Skelaxin®)

- **Metaxalone** is a ***muscle relaxant*** **agent**.
- ***Mechanism of action***; **unknown**, but may be ***due*** to ***general*** **CNS depression**.
- ***Uses***; as an ***adjunct***, for the ***relief*** **muscle spasms*** *associated with* ***acute painful*** **musculoskeletal conditions**.
- ***Dose***; 800 mg 3-4 times daily.
- ***Side effects***; **Drowsiness, dizziness, nausea** and **vomiting**.
- ***Contraindications***; ***severe*** **hepatic** and **renal dysfunction**.

Chlorzoxazone (Parafon®)# (Myofen®)#

- **Chlorzoxazone** is a ***muscle relaxant*** **agent**.
- ***Mechanism of action***; ***Not fully understood***, but it ***works*** **primarily** in **spinal cord** and **subcortical areas** of the brain ⇨ ***inhibits*** **multi-synaptic reflex arcs** involved in ***producing*** and ***maintaining*** **skeletal muscle spasm**.
- ***Uses***; **symptomatic *treatment*** of **muscle spasms*** and **pain** *associated with* ***acute painful*** **musculoskeletal conditions**.

Chlorzoxazone is ***available*** in a ***combination*** with **analgesics** to ***relief*** **pain** *associated with* **muscle spasms**; **NSAIDs (Ibuprofen; Myofen®)** or with **Paracetamol (Parafon® - Myolgin®)**.

- ***Dose***; 250-750 mg orally 3 to 4 times daily.
- ***Side effects***; **Dizziness, lightheadedness, malaise, nausea** and **vomiting**.
- ***Warning***; **Serious** (or **fatal**) **hepatocellular toxicity**, ***especially*** if used with **Paracetamol**.

B) Peripherally Acting Skeletal Muscle Relaxants

Neuromuscular Blockers (NMBs)

- These drugs **block cholinergic transmission** between ***motor nerve endings*** and the ***nicotinic receptors on the skeletal muscle***.
- NMB are clinically useful **during surgery** to facilitate tracheal intubation and provide ***complete muscle relaxation*** at lower anesthetic doses (*lower anesthetic doses*; allowing for more rapid recovery and reducing postoperative respiratory depression).
- ***Uses***;
  - **Surgical relaxation**; As adjuvants during general anaesthesia.
  - **Endotracheal intubation**; by relaxing pharyngeal and laryngeal muscles.
  - **Electro-convulsion therapy (ECT)**; to control muscle contraction.

- ***Classification according to mechanism of action***;

Non-Depolarizing NMB (Competitive)		
Tubocurarine (Tubarine®)	**Atracurium** (Tracrium®)	**Cisatracurium** (Nimbex®)
Mivacurium (Mivacron®)	**Doxacurium** (Nuromax®)	**Metocurine** (Metubine®)
Rapacuronium (Raplon®)	**Rocuronium** (Esmeron®)	**Vecuronium** (Norcuron®)
Pancuronium (Pavulon®)	**Pipecuronium** (Arduan®)	**Gallamine** (Flaxedil®)

- **Curare** is the ***first drug*** known to block the skeletal NMJ, which native South American hunters of the Amazon region used to paralyze prey.
- **Tubocurarine** is the ***active agent*** of one of the forms of **Curare**, but it has been ***replaced by*** **other agents** with ***fewer*** **side effects**.

Atracurium is an ***intermediate*-duration of action**, it ***cause slight*** **histamine release** (***hypotension*** and ***bronchospasm***) and is ***metabolized to*** **toxic metabolite** called **Laudanosine** ⇨ which can cause ***seizures***. It has been ***replaced by*** its isomer ⇨ **Cisatracurium**.

Cisatracurium is ***one isomers*** of the **Atracurium**, one of the ***most commonly used*** (***most popular***) and it have ***fewer side effects*** *than* **Atracurium** (***less*** **histamine release** & ***less*** **Laudanosine**).

Mivacurium is a ***shortest*-duration of action** of ***all*** **non-depolarizing NMB**, it ***cause*** **histamine release**. ***Clearance by*** **plasma cholinesterase enzyme** and may be ***prolonged*** in **patient with impaired renal function** (due to; decrease in cholinesterase enzyme). ***No longer used***.

Doxacurium is use has ***not been popular*** because of ***considerably*** **long duration of action**, ***cause*** **histamine release** and ***metabolized into*** **Laudanosine**, ***greater accumulation*** in **individuals** with **renal failure**.

Rapacuronium ***is a*** ***short*** **acting amino-steroid compounds** and ***used in short*** **surgical operation**, ***side effects*** *include*; **hypotension**, **tachycardia** and **fatal bronchospasm**.

- **Rocuronium** and **Vecuronium** are ***metabolized in*** the **liver** and ***clearance*** *may* be ***prolonged*** in *patient with* **hepatic disease**.
- **Pancuronium** is the one of three drugs administered during most **lethal injections**.

Gallamine ***cause*** **tachycardia** and occasionally ↑ in **blood pressure** ***because***; **1)** it has strong **parasympatholytic effect** on the cardiac vagus nerve (Atropine like effect on the heart via block M_2 receptors). **2)** It has **sympathomimetic effect** via ↑ **norepinephrine (NE)** release (Tyramine like effect). It has ***no*** **histamine release**.

All neuromuscular-blockers are ***highly*** **polar** (*not pass* **BBB**) and ***inactive*** **orally**; they **must be administered** ***parenterally***.

- **Atracurium** and **Cisatracurium** can be used in **renal** and **hepatic** ***impairment***.

Side effects; - **Tubocurarine > Mivacurium > Atracurium ⇨ Hypotension.**
- **Gallamine > Pancuronium ⇨ Tachycardia.**

Drug interactions;

- **Cholinesterase inhibitors**; *such as* **Neostigmine** and **Physostigmine**; overcome the action.
- **Inhaled anesthetics**; *such as* **Halothane** and **Desflurane**; enhance NMB effect.
- **Aminoglycoside antibiotics**; *such as* **Gentamicin** and **Tobramycin**; ***Synergistic effect***.
- **Calcium channel blockers**; enhance NMB effect.

Depolarizing NMB (Non-Competitive)

Succinylcholine (Succinylcholine®) | **Decamethonium** (Syncurine®)

Side effects; **Prolonged apnea**, **bradycardia**, **myalgias**, *increase* **IOP**, and **hyperkalemia** and **malignant hyperthermia**.

Botulinum Toxin (BTX)

***Clostridium botulinum* toxin type A** (Botox®)#

- **Botulinum toxin** is a ***neurotoxic*** **protein** *produced by* the **bacterium** ***Clostridium botulinum***.

Botulinum toxin is the ***most powerful*** **neurotoxin** *known to date* (Only one single molecule of it is needed to stop one neuron working. *In fact*, 1 gram of botulinum toxin would be enough to kill 14,000 people (if ingested), 1.25 million people if inhaled, or a staggering 8.3 million people if injected).

- ***Clostridium botulinum*** is an **anaerobic**, **Gram positive**, **spore**-*forming* **rod**.
- **Botulinum toxin** acts by ***blocking*** **nerve function** by ***inhibition*** **Acetylcholine** ***release*** from the **presynaptic neuromuscular junctions**. This causes **skeletal muscle** ***paralysis*** and **respiratory failure** by paralysing the muscles of the chest.
- There are **2 commercial types** of **BTX**; **Botulinum toxin type A** and **Botulinum toxin type B**.

Most common applications (***Uses***) or **Botulinum toxin type A** (**Botox®**);

Cosmetics; ***Prevent*** **development** of **wrinkles** by paralyzing facial muscles.

Medical uses; **Muscle spasticity***, **dystonia**, **overactive bladder**, **chronic migraine**, **axillary hyperhidrosis**, **blepharospasm**, **strabismus**, and **anal fissure**.

Botulinum toxin type B (**Myobloc®**); used in **cervical dystonia**.

- **Heptavalent Botulism AntiToxin** (**HBAT**); was approved in 2010 as **botulism antitoxin** that effectively neutralizes all 7 known botulinum nerve toxin serotypes (types A, B, C, D, E, F and G).

C) Direct Acting Skeletal Muscle Relaxants

Dantrolene (Dantrium®)# (DantRelax®)#

Dantrolene is a ***hydantoin derivative*** related to **Phenytoin** that has a ***unique peripheral mechanism*** of ***spasmolytic activity***.

Mechanism of action; **Dantrolene** is the ***only*** (***unique***) **drug** available that ***inhibits*** Ca^{2+} ions ***release*** from **sarcoplasmic reticulum**.

Uses; - ***Treatment*** of **chronic muscle spasticity*** of upper **neuronal disorders**, including spinal cord injury, multiple sclerosis, and cerebral palsy.

- ***Dose***; 25 mg orally once daily for 7 days, then 25 mg three times a day for 7 days, then 50 mg three times a day for 7 days, then 100 mg three times a day.

- **Malignant hyperthermia**;
  - ***Dose***; **IV**; bolus 2.5 mg/kg, then 1 mg/kg IV every 4-6hr OR 0.25 mg/kg/hr IV infusion.

- ***Most common side effects***; drowsiness, dizziness, fatigue and diarrhea.
- ***Black box warning***; ***potential for*** **hepatotoxicity**.

Drugs for Gout and Hyperuricemia

Gout is a ***sudden***, ***severe*** **attacks** of **pain**, **redness** and **tenderness** in **joints** (often **big toe**).
Hyperuricemia; is an ***abnormally*** **high level** of **Uric Acid** (**UA**) in the **blood**;
Reference range; **Male**; 3.5–8.0 mg/dL. **Female**; 2.5–6.5 mg/dL.
Gout Risk Factors; # # # # # # # # **PATIENT COUNSELLING** # # # # # # #

- ***Alcohol Consumption***; ***higher risk*** of **incident gout** & ***higher rate*** of **gout flares**.
- ***Dietary***;

** *Avoid*;	** *Limit*;
- **Organ meats**; Liver, kidneys, brain & heart.	- **Meat**; beef, lamb chicken, pork.
- **Game** (hunting) **meats**; rabbit and venison.	- **Poultry**; chicken and duck.
- **Fish**; herring, mackerel and sardines.	- **Dried peas**, **beans** and **legumes**.
- **Seafood**; mussels, shellfish and caviar.	- **Mushrooms**.
- **High-fructose drinks or foods**.	- **Some vegetables**; cauliflower and spinach.

- ***Drugs***;
  - **Thiazide** & **loop diuretics** (***higher risk*** of **incident gout** & ***higher rate*** of **gout flares**).
  - ***Low-dose*** **Aspirin** (***may also*** be a ***risk factor*** for **gout**).
  - **Xanthine oxidase inhibitors** (**XOIs**) and **uricosuric agents**; ***only in initial therapy***.
- ***Medical conditions***; **Hyperuricemia**, **obesity**, **diabetes**, **hypertension**, **dyslipidemia**, **renal insufficiency** and **early menopause**.
- ***Other conditions***; **Trauma**, **surgery**, **starvation**, **dehydration** and **family history**.

Non-pharmacological Therapy

- **Dietary Modifications** (*see risk factors*).
- **Maintaining adequate fluid intake**.
- **Weight loss** (*if obese*).
- **Exercise** (regular aerobic exercise program).
- **Smoking cessation**.

Pharmacological Therapy

Drugs for Gout Attacks

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

Indomethacin (Indocid®)#	**Naproxen** (Aleve®)#	**Sulindac** (Clinoril®)#

NSAIDs are the ***first-line treatment of*** **acute gouty attacks**.
Indomethacin has been ***historically favored*** as **NSAID** of ***choice for*** **acute gout**.
- ***Only*** **FDA-approved**; **Indomethacin**, **Naproxen** and **Sulindac** for the ***treatment of*** **acute gouty attacks**, **BUT** ***other*** **NSAIDs** *may be* as **effective**.
- **Celecoxib** is an ***option*** in ***patients*** with ***contraindications*** or ***intolerance*** to **NSAIDs**.

Common Side Effects; **GIT** (gastritis and bleeding), **kidneys** (renal dysfunction), **CVS** (risk of CV events in susceptible patients and hypertension).
Consider **co-administration** with a **proton-pump inhibitor** (**PPI**) for ***patients*** at ***risk for*** **gastrointestinal bleeding**.

Colchicine

Colchicine (Colchicine® 500 mcg)#

Colchicine, is an *antimitotic drug*, is a *plant alkaloid*, *used for* the *treatment of* acute gouty attacks and familial Mediterranean fever (FMF).

Colchicine *relieves* the pain and inflammation of **gouty arthritis** in **12–24 hours** *without* *altering* the **metabolism** or **excretion** of **urates** and *without* *other analgesic* **effects** (*not an analgesic*).

- Colchicine is used *less often than* **NSAIDs**, and *may be* reserved as a **second-line therapy** when **NSAIDs** are *contraindicated* or *ineffective*.

Side Effects; - *Dose-related GI side effects*; **nausea**, **vomiting** & **diarrhea** (50-80%).
- *Chronic use*; **myopathy**, **neutropenia**, **aplastic anemia** and **alopecia**.

Dose; *Recently*, **lower dose of colchicine** are used; **1.2 mg**; *then* **0.6 mg 1 hour** *later*; *then* **0.6 mg** *once* or *twice* **daily** *until* **attack resolves** (Colchicine *was* used in **higher doses**, *hourly* **dosing** *until* **gastrointestinal symptoms** *become develops* such as **diarrhea**).

Contraindications; *Co-administration* of Colchicine with *strong* **CYP3A4 inhibitors** (Erythromycin or Clarithromycin) in **renal** or **hepatic impairment** (*fatal toxicity*).

Corticosteroids (CSs)

- **Corticosteroids** *may be* an *appropriate alternative* for **patients** who *cannot* **tolerate** **NSAIDs** or Colchicine, *however*, *recent* **evidence** *indicates* that **corticosteroids** are *equivalent to* **NSAIDs** in the *treatment* of **acute gout flares**.

1) **Oral corticosteroid** (**OCS**) *used for* *all* **cases of gout** (**oral route** is a *first-line*);
   - **Prednisone** 0.5 mg/kg (30-60 mg) per day for 5–10 days.
     OR (*to reduce the risk of a rebound flare*), **Prednisone** 0.5 mg/kg for 2–5 days, then *tapered gradually* over 10 to 14 days, then discontinue (i.e.; 40 mg for 4 days, then 20 mg for 4 days, then 10 mg for 4 days).
   - **Methylprednisolone** **Dose Pack**; Six days of pre-dosed 4 mg package.
2) **IM corticosteroid**; *Single dose* of **Triamcinolone** (60 mg) *followed by* **OCS**.
3) **Intra-articular corticosteroid**; **Triamcinolone** is *limited to* **one** or **two large joints**;
   - **Large joint**; 40 mg of **Triamcinolone**. - **Medium joint**; 30 mg of **Triamcinolone**.
   - **Small joint**; 10 mg of **Triamcinolone**.

- *N.B.*; **Intra-articular CSs** *can be* **used in** ***combination with*** **OCSs**, **NSAIDs** or **Colchicine**.

Drugs for Gout Prevention and Hyperuricemia

Xanthine Oxidase Inhibitors (XOIs)

Allopurinol (Zyloric®)# (Zyloprim®)

Allopurinol, a *xanthine oxidase inhibitor*, is a *purine analog*; *decrease* **Uric Acid** **production** by *competitively inhibiting* **xanthine oxidase** *enzyme*.

Uses; **Gout** and **hyperuricemia** *secondary to* **chemotherapy**.

- *Dose*; - *Starting Dose*; < **100 mg/day**; *Reduces* **early gout flares** and *risk* of **hypersensitivity syndrome**.
  - *Dose Titration*; *gradually titrate* dose **every 2–5 weeks**.
  - *Maintenance Dose*; can be *higher than* **300 mg daily**.

- *Side effects*; *About* **20% of patients** on **Allopurinol** report *side effects*;
  - *GI Side Effects*; **Nausea**, **vomiting**, and **diarrhea**.
  # # # **Allopurinol hypersensitivity syndrome (AHS)**; *Mortality; 20–25%.*
  - *Severe* **hypersensitivity reactions**; **urticaria**, **Stevens-Johnson syndrome**, **hepatotoxicity** and **eosinophilia**.

- *Drug interactions*; **6-mercaptopurine**, **Azathioprine** and **Theophylline**

Febuxostat (Uloric®)# (Feburic®)#

- **Febuxostat**, a ***xanthine oxidase inhibitor***, is ***structurally unrelated*** to **Allopurinol**.
- ***Mechanism***; ***Selective*** **direct non-competitively blocking** of **xanthine oxidase**.

Febuxostat VS Allopurinol;

- ***Cost***; **Febuxostat** ***more expensive***.
- ***Mechanism***; - **Allopurinol**; **Competitive**. - **Febuxostat**; **Non-competitive**.
- ***Side effects***; **Allopurinol** ***more severe***.
- **Chronic Kidney Disease**; **Allopurinol** require dose adjustment.

- ***Dose***; - **Febuxostat** is *approved at doses* of 40, 80 or 120 mg.
  - ***Starting dose***: 40 mg once daily.
  - ***If goal serum urate not reached***; dose may increase dose to 80 mg once daily.
- ***On*** **February 21, 2019 FDA** ***concluded*** there is an ***increased*** **risk of death** with **Febuxostat** ***compared to*** *another* **gout medicine** such as **Allopurinol**.
- ***N.B.***; Use with caution in severe renal impairment (CrCl <30 mL/minute); insufficient data.

Uricosuric Agents

- ***Uricosuric Agents***; are **substances** that ***increase*** the **excretion** of **Uric Acid** in the ***urine***.

Probenecid | Sulfinpyrazone (Anturane®)

- ***Indications***; ***If*** **XOIs** **is** ***contraindicated*** **or** ***not tolerated***.
- ***Dose***;- **Probenecid**; ***Initial***; **250 mg** ***twice*** a **day** for **1-2 weeks** and then **500 mg** ***twice*** a **day** for **2 weeks** (when initiating, increase fluid intake or urine alkalinization).
  - **Sulfinpyrazone**; ***Initial***: 100-200 mg ***twice***, *with* **meals** or **milk**, ***gradually*** **increasing** ***when*** **necessary** to ***full*** **maintenance dosage** (200-400 mg ***twice***) **in 1 week**.
- ***Most Common Side Effects***; **GI disturbances**.
- ***Contraindications***; **Probenecid** ***contraindicated*** in **patients** *with* **CrCl** < 50 mL/min.
- **Secondary Uricosurics** *(second-line)*; **Losartan** and **Fenofibrate** *(off-label use)*.

Selective Uric acid Reabsorption Inhibitor (SURI)

Lesinurad (Zurampic®)

- ***Approval***; ***FDA*** approval on December, 2015. ***European Union*** on February 2016.
- ***Indications***; In ***combination with*** a **xanthine oxidase inhibitor (XOI)** for the ***treatment of*** **hyperuricemia** ***associated with*** **gout** in ***patients*** who have ***not achieved*** **target serum uric acid levels** with a **xanthine oxidase inhibitor** ***alone*** [**NOT USED ALONE**].
- ***Recommended Dose***; **200 mg once daily** in ***combination with*** a **xanthine oxidase inhibitor**, including **Allopurinol** or **Febuxostat**.
- ***Contraindications***; - **Severe renal impairment** (CrCl less than 30 mL/min).
  - **Tumor lysis syndrome (TLS)** or **Lesch-Nyhan syndrome**.
- ***FDA WARNING***; - **Renal events** (**acute renal failure** ***more common*** when **used alone**).
  - **Cardiovascular events**.

Recombinant Urate Oxidase (UO) "Uricase"

- **Urate Oxidase (UO)** ***enzyme*** or **Uricase**, is ***absent*** in **humans** (found nearly all organisms except humans) and ***catalyzes*** the ***oxidation*** of **Uric Acid** ***to*** **Allantoin**.
- **Allantoin** is an ***inactive*** (nontoxic) and ***more soluble*** **metabolite** and ***easily*** **excreted**.

Pegloticase (Krystexxa®)#

- ***Indications***; ***treatment of*** **severe**, **refractory** or **resistant chronic gout**.
- ***Dose***; 8 mg IV infusion every 2 weeks.

 # FDA warning; **Anaphylaxis** and **infusion reactions** and ***Life-threatening*** **hemolysis**.

Rasburicase (Elitek®)#

- ***Indications***; ***Prevention*** & ***ttt*** of **hyperuricemia** ***caused by*** **Tumor Lysis Syndrome**.
- ***Dose***; 0.2 mg/kg as a 30-minute IV infusion once a day for up to 5 days.

 # FDA warning; **Anaphylaxis** and **infusion reactions** and ***Life-threatening*** **hemolysis**.

Disease Modifying Antirheumatic Drugs (DMARDs)

Disease Modifying Antirheumatic Drugs (DMARDs) [dee-MAAR-D]; Used for **rheumatoid arthritis**.

1) **Non-biologic DMARDs**;
   - ***Most common***; **Methotrexate**, **Leflunomide**, **Hydroxychloroquine** and **Sulfasalazine**.
   - ***Less common***; *such as*; **Gold Salts**, **Azathioprine**, **Cyclosporine** and **D-Penicillamine**.
2) **Biologic DMARDs**;
   - ***TNF inhibitors***; **Etanercept**, **Adalimumab**, **Infliximab**, **Certolizumab** & **Golimumab**.
   - ***Non-TNF Biologic***; **Abatacept**, **Rituximab**, **Anakinra**, **Tocilizumab** and **Tofacitinib**.

Disease Modifying Antirheumatic Drugs (DMARDs)

Non-biologic (Traditional) DMARDs

Methotrexate (Methotrexate®)

- **Methotrexate** (**MTX**) is a ***synthetic antimetabolite*** (**Folic acid *antagonist***).
- It was ***originally used as*** a **chemotherapy *treatment for* cancer** (first made in 1947), ***used in much lower doses*** for **rheumatoid arthritis** and ***other*** **rheumatic diseases** (such as systemic lupus erythematosus and Sjögren's syndrome).

MTX *now considered* the ***first-line*** **DMARD** for ***treatment of*** **rheumatoid arthritis**.

- **MTX** may be ***combined with other*** **DMARDs** or ***with*** a **biologic agent** if **MTX** **alone *does not*** **adequately control a patient's disease**.
- ***Uses***; 1) ***Cancer Chemotherapy***; **MTX** is an ***antimetabolite*** used in the *treatment of* ***certain*** **cancers**.
  2) ***Autoimmune Diseases***; **MTX** is used as a ***disease-modifying agent*** for *some* **autoimmune diseases**, including; **rheumatoid arthritis**, **juvenile dermatomyositis**, **psoriasis**, **psoriatic arthritis**, **lupus**, **sarcoidosis**, **Crohn's disease**.
  3) ***Abortion***; US FDA pregnancy **category X**; **MTX** is an ***abortifacient agent*** during the ***early stages***, *generally* in ***combination with*** **Misoprostol**. It is ***used to treat*** **ectopic pregnancies**.
- ***Dose***; *Doses of* **MTX** *required for* **RA** treatment are ***much*** **lower than** those needed in **cancer chemotherapy** and are given ***once*** a **week**, *thereby* ***minimizing*** **adverse effects**;
  - **MTX** may be given **IM**, **SC** or **orally**.
  - ***Dosing regimen for*** the treatment of **RA** **7.5-15** mg ***once*** a **week**.
  - ***Onset of effect***; *within* **3-6 weeks** of ***starting*** **treatment**.

Side effects; - ***Most common***; **Mucosal ulceration** and **nausea**.
- ***Other side***; **leukopenia**, **anemia**, **stomatitis**, **GI ulcerations** and **alopecia** (*due to inhibiting cellular proliferation*), **halitosis** (bad breath odour).
- ***Dose-related side effects***; **hepatotoxicity**.
- ***Rare side effects***; **acute pneumonitis** and **kidney failure**.

- ***Monitoring***; **Liver enzyme tests**, **complete blood counts**, and **monitoring *for* signs of infection**.

Taking **Folinic acid** (**leucovorin®**) **24 hours *after*** *each* **weekly dose** or by the use of ***daily*** **Folic acid** (not in the same day; ***off-days***), although this may ***decrease*** the **efficacy** of **Methotrexate** by about 10%, ***but*** this ***reduces severity*** of **adverse effects**.

N.B.; **Folinic acid *should be distinguished from* Folic acid**. **Folinic acid *does not*** require the action of **dihydrofolate reductase** for its ***conversion***.
- **Levoleucovorin** (**Fusilev®**) is an **enantiomerically *active form*** of **Folinic acid**.

- ***Drug Interactions***; **Penicillins**, **Aminoglycosides**, **Omeprazole**, **Valproate** & **NSAIDs**

Leflunomide {Original brand (Arava®)#} {Egypt brand (Avara®)#}

- **Leflunomide**, ***like* MTX**, is an ***immunomodulatory non-biologic* DMARD**.
- **Arava®** was developed by Sanofi Aventis and approved by the US FDA in 1998.
- **Leflunomide** has ***efficacy similar to* MTX** for ***treating* RA**.
- **Teriflunomide** (***active metabolite of* Leflunomide**) was approved by the FDA in 2012 for the ***treatment of patients with* relapsing forms of multiple sclerosis (MS)**.
- ***Dose***; - ***Loading dose***: **100 mg** orally ***once*** a **day** for **3 days**.
  - ***Maintenance***: **20 mg** orally ***once*** a **day** (may be decreased to 10 mg orally once a day).

Most common side effects (up to 10%); **Respiratory infection, diarrhea, nausea, headache, hypertension, alopecia, rash, weight gain** & ***abnormal* liver function tests**.

Pregnancy; **Category X** (**Leflunomide** and **Teriflunomide**); **# PRECAUTIONS #**

- Women should wait to become pregnant for at least 2 years after discontinuation of treatment and plasma levels of A771726 should be less than 0.02 mg/L).
- ***Or*** Administer **Cholestyramine** 8 grams, 3 times daily for 11 days, verify plasma levels less than 0.02 mg/L by 2 separate tests at least 14 days apart. If plasma levels are higher than 0.02 mg/L, additional **Cholestyramine** treatment should be considered.
- Men who are planning parenthood and are being treated with Leflunomide should undertake **Cholestyramine** washout and wait for at least one and possibly three spermatic cycles before inseminating their spouse.

Hydroxychloroquine (Plaquenil®)#

- **Hydroxychloroquine** is an ***antimalarial drug***.
- ***Onset of effects***; **6 weeks** to **6 months** (> 6 months without a response = therapeutic failure).
- ***Main advantage***; ***less toxicities*** on the **liver**, **kidney** and **immune system** than ***other* DMARDs**, which *simplifies* **monitoring**.

Hydroxychloroquine is very ***extensively* tissue-bound**, particularly in ***melanin-containing* tissues** such as the **eyes** (**OCULAR TOXICITY**).

- ***Dose*** in **RA**; Oral: 200-300 mg twice daily, after 1–2 months may to 200 mg twice or once daily.
- ***Most common side effects***; **GI effects**; *mild* **nausea, dyspepsia**, and **diarrhea** (can be managed by taking doses with a food or a glass of milk). ***Chronic use side effects***; **skin pigmentation, hair bleaching, alopecia skin rash** and **CNS disturbances**.

Serious side effects; ***Ocular toxicity***; accommodation defects, benign corneal deposits, blurred vision, scotoma (small areas of decreased or absent vision in the visual field) and night blindness.

Monitoring; **Ophthalmoscopy** every 9–12 months and Amsler grid test at home every 2 weeks.

- ***Contraindications***; **G6PD deficiency**, **retinal** or **visual field changes** and ***long-term* in children**.
- **N.B.**; **Chloroquine** is ***another antimalarial agent*** that is also ***sometimes* used**.

Sulfasalazine (Azulfidine®)

- **Sulfasalazine** (**SSZ**) is a ***prodrug***, is a ***sulfa drug*** *cleaved by* **bacteria** in the **colon** into **Sulfapyridine** and **Mesalazine** (**5-Amino-Salicylic Acid**; **5-ASA**).

Sulfapyridine is *probably* the ***active moiety*** in ***treating* RA** (***unlike* inflammatory bowel disease**, **Mesalazine** (**Pentasa®**) is the ***active moiety*** in treating this disease).

- ***Dose*** in **RA**; **500 mg** to **1 g** ***twice daily***.
- ***Most common side effects***; **nausea, vomiting, headache** and **rash**.
- ***Contraindications***; **G6PD deficiency**, or ***hypersensitivity*** to **sulfa drugs** and **urinary obstruction**.
- ***Drug interactions***; **Warfarin, oral hypoglycemic, antibiotics** and **iron supplements**.

Other Non-biologic DMARDs

Gold Salts	**Cyclophosphamide** (Cytoxan®)# (Endoxan®)#
Chlorambucil (Leukeran®)#	**Azathioprine** (Imuran®)#
Cyclosporine (Sandimmune Neoral®)#	**D-penicillamine** (Artamin®)#

- ***Although*** **these drugs** can be ***effective***, **BUT** they are **used** ***less frequently*** **today** *because of* **toxicity**, ***lack of*** **long term benefit or both**.

Cyclophosphamide (**Endoxan®**); ***Alkylating Agent***.
- ***Uses***; **Certain cancers** and **autoimmune diseases**.
- ***Side effects***; **Nausea, vomiting,** ***increased risk of***; **developing certain cancers** and **risk** of **infections, anemia** (bone marrow suppression), **alopecia** and **infertility** (in males and females).

Chlorambucil (**Leukeran®**); ***Alkylating Agent***.
- ***Uses***; **Certain cancers** and **autoimmune diseases**.
- ***Side effects***; **Nausea, vomiting,** ***increased risk of***; **developing certain cancers** and **risk** of **infections, anemia** (bone marrow suppression), **alopecia** and **infertility** (in males and females).

Azathioprine (**Imuran®**); ***Immunosuppressive Drug***.
- ***Uses***; **Organ transplantation** and **autoimmune diseases**.
- ***Side effects***; **Nausea, vomiting, hepatitis, pancreatitis,** ***increased risk of***; **infections** & **developing certain types of cancers**.

Cyclosporine (**Sandimmune Neoral ®**); ***Immunosuppressive Drug***.
- ***Uses***; **Organ transplantation** and **autoimmune diseases**.
- ***Side effects***; **Nausea, vomiting, hepatitis, pancreatitis,** ***increased risk of*** **infections**.

D-Penicillamine (**Artamin®**); ***Chelating Agent*** (Chelates gold, copper, mercury and arsenic).
- ***Uses***; **Wilson disease** (accumulation of copper in tissues) and **rheumatoid arthritis**.
- ***Side effects***; **Nausea, vomiting, diarrhea** and **bone marrow suppression**.

Biologic DMARDs

- **Biologic DMARDs** are ***genetically engineered*** **protein molecules** that ***block*** the **proinflammatory cytokines**;

* ***These drugs*** may be ***effective*** *when* ***other*** **DMARDs** (non-biologic) ***fail*** to ***achieve*** **adequate responses** but are ***considerably*** **more expensive** ***to use***.

* ***Most*** of **these drugs** are ***increased*** an ***incidence*** of ***risk of*** **tuberculosis infection** (tuberculin skin testing is recommended).

* **Live vaccines** ***should not*** be **given** to ***avoid*** the **risk** of **infection**.

TNF-α Inhibitors

Tumor necrosis factor alpha (**TNF-α**) is a ***pro-inflammatory cytokine*** *produced by* **macrophages** and **lymphocytes**. It is *found in* ***large quantities*** in **rheumatoid joint**.

TNF ***antagonists*** were the ***first*** of **biological DMARDs** approved for **RA**.

Anti-TNF agents began to ***enter the market*** for **RA** in **1999**.

There are ***currently*** **5 TNF inhibitors** FDA *approved for* **RA**; listed in order of their approval for **RA**; **Etanercept**, **Infliximab**, **Adalimumab**, **Certolizumab** & **Golimumab**.

Anti-TNF PRECAUTIONS

Risk of **serious infections**, or ***history of*** **recurring infections**; **black box warning**.
Recent malignancies; *especially* **lymphoproliferative cancer**; **black box warning**.
Congestive heart failure (**CHF**); New York Heart Association (NYHA) class III or IV heart failure
Demyelinating diseases; *like* **multiple sclerosis**.
Avoid **vaccination** *with* **live vaccines**.

- ***Response*** was seen in **60-75%** of **patients**.
- ***Onset of effect***; ***rapid onset of action*** sometimes with **improvements** seen ***within*** **2-4 weeks**, however, ***additional improvements*** can be seen ***over*** **3-6 months**.
- ***Pregnancy***; **category B**.
- The global market for TNF inhibitors in 2008 was $13.5 billion and $22 billion in 2009.

Etanercept (Enbrel®)#

- **Etanercept** is a ***recombinant***, ***fully*** **human receptor** ***fusion*** **protein**.

Indications; **RA**, **ankylosing spondylitis**, **psoriasis** and **psoriatic arthritis**.

- ***Dose***; **25 mg SC** ***twice*** **weekly** or **50 mg SC weekly**.

Methotrexate, **Glucocorticoids** or **NSAIDs** ***may be*** **continued** ***during*** **treatment** (70% of patients taking **Etanercept** are also using **Methotrexate**).

** ***Precautions*** or ***Contraindications***; ***increase*** *risk for* **infections**, **malignancy** and **worsening heart failure** (**DON'T** ***forget*** the **anti-TNF precautions**).

Infliximab (Remicade®)#

- **Infliximab** is a ***recombinant*** **DNA-derived** **chimeric** **human-mouse** **IgG_1 monoclonal antibody**.

Indications; **RA**, **Crohn's disease**, **ulcerative colitis**, **psoriasis**, **psoriatic arthritis** and **ankylosing spondylitis**.

- ***Dose***; 3–5 mg/kg **IV** at 0, 2, and 6 weeks, then every 8 weeks; may be increased to 10 mg/kg.
- ***N.B.***; The **immune system** in **patients** *treated with* **Infliximab** ***may develop*** **antibodies** to this ***foreign*** **protein** of **Infliximab** (*called* **anti-infliximab antibodies**); ***reduced efficacy***.

Methotrexate ***should be*** **given** *as long as* ***with*** **Infliximab** to ***decrease*** or ***prevent*** the ***formation*** of **anti-infliximab antibodies**.

- **Infusion site reactions** ***may*** **occur** and may ***correlate with*** **anti-infliximab antibodies** ***formation*** (antihistamines may prevents some of these reactions).

** ***Precautions*** or ***Contraindications***; ***Like other*** **TNF-α blocking agents**.

Adalimumab (Humira®)#

- **Adalimumab** is a ***recombinant*** ***fully*** **human IgG_1 monoclonal** ***antibody***.
- ***Mechanism***; ***Like*** **Infliximab**, *but* **Adalimumab** is ***fully*** **human** (***not*** **chimeric**), ***no*** **foreign protein** in **Adalimumab**, is ***less*** ***antigenic than*** **Infliximab**.

Indications; **RA**, **Crohn's disease**, **ulcerative colitis**, **psoriasis**, **psoriatic arthritis** and **ankylosing spondylitis**, **hidradenitis suppurativa** and **juvenile idiopathic arthritis**.

- ***Dose***; ***usual dose*** is 40 mg **SC** every other week (14 days).

** ***Precautions*** or ***Contraindications***; ***Like other*** **TNF-α blocking agents** (*serious TB infection*).

Golimumab (Simponi®)#

- **Golimumab** is a ***human*** **monoclonal antibody** with a ***high*** **affinity** for ***soluble*** and ***membrane-bound*** **TNF-α**.

Indications; **RA**, **ulcerative colitis**, **psoriatic arthritis** and **ankylosing spondylitis**.

- ***Dose***; - **Simponi®**; 50 mg **SC** monthly.
  - **Simponi® Aria**; 2 mg/kg IV infused over 30 minutes at weeks 0 and 4, then every 8 weeks.

** ***Precautions*** or ***Contraindications***; ***Like other*** **TNF-α blocking agents**.

Certolizumab Pegol (Cimzia®)#

- **Certolizumab** is a ***unique*** **TNF-α blocker** that contains a ***recombinant***, ***humanized*** **antibody Fab fragment** ***conjugated to*** a **Polyethylene Glycol** (**PEG**) (not contain **IgG_1**) with ***specificity*** for ***human*** **TNF-α**.

Indications; **RA**, **Crohn's disease**, **psoriatic arthritis** and **ankylosing spondylitis**.

- ***Dose***; 400 mg **SC** initially and repeat at weeks 2 and 4, followed by 200 mg every other week or 400 mg every 4 weeks.

** ***Precautions*** or ***Contraindications***; ***Like other*** **TNF-α blocking agents**.

T-Cell Activation Blockade

Abatacept (Orencia®)#

- **Abatacept** is a ***soluble recombinant*** **fusion protein** *composed of* the **Fc region** of the **immunoglobulin IgG_1** ***fused to*** the **extracellular domain** of **CTLA-4** (**CTLA4-Ig**).

Indications; ***Monotherapy*** (***first-line therapy***) or in ***combination*** (*not with other biologic drugs*) with ***other*** **DMARDs** in patients with ***moderate*** to ***severe*** **rheumatoid arthritis**.

Abatacept may use in **autoimmune type 1 diabetes** to ***protect*** surviving **beta cells** from **autoimmune** ***attack***.

- ***Dose***; **IV infusion** based on patient weight (<60 kg; 500 mg. 60–100 kg; 750 mg. >100 kg; 1,000 mg) every 2 weeks for two doses after and then every 4 weeks.
- ***Pregnancy***; **category C**.
- ***Common side effects***; **headache**, ***upper*** **respiratory infections**, **nasopharyngitis** and **nausea**.

N.B.; ***Concomitant use*** **Abatacept** with **anti-TNF-α** is ***not recommended*** due to the ***increased incidence*** of **serious infection**.

B-Cell Depletion

Rituximab (Rituxan®)#

- **Rituximab** is a ***genetically engineered chimeric*** (murine/human) **monoclonal antibody** directed ***against*** the **CD20 antigen** *found on* the ***surface*** of **normal** and **malignant B lymphocytes**, ***resulting*** in **B-cell depletion**. **Rituximab** ***was originally*** *developed to* treat **non-Hodgkin's lymphoma**.

Indications; **Hematological cancers**, **autoimmune diseases** and **organ transplantation**.

- ***Dose***; in **RA**; Two infusions of 1,000 mg are given 2 weeks apart. **Methylprednisolone** 100 mg should be given 30 minutes prior to reduce the incidence and severity of infusion reactions.

Recommendations; **Rituximab** is used in ***combination*** with **Methotrexate** in patients who ***failed to*** **one** or **more** ***types*** of **treatment** (***including anti-TNF***).

- ***Pregnancy***; **category C**.

Common side effects; **Infusion reactions** (urticaria, hypotension and angioedema).

IL-1 Inhibitors

Anakinra (Kineret®)#

- **Anakinra** is a ***recombinant*** **IL-1 receptor** ***antagonist*** (*E.coli-derived product*).

Indications; **RA** and **neonatal-onset multisystem inflammatory disease** (**NOMID**).

- ***Recommendations***; The **American college of rheumatology** ***guidelines did not include*** **Anakinra** in ***their*** **RA** ***treatment recommendations*** *due to* its ***infrequent*** **use** in **RA** and ***lack of*** **new data** since 2012, ***but some patients*** could ***benefit*** from **treatment** with ***this*** **drug** (patients who have failed one or more DMARDs).
- ***Dose***; 100 mg SC daily.
- ***Pregnancy***; **category B**.

** ***Precautions*** or ***Contraindications***; **Neutropenia**, ***severe*** **renal impairment**, *increased* **risk for infections** and **malignancy**.

IL-6 Inhibitors

Tocilizumab (Actemra®)#

- **Tocilizumab** is a ***humanized*** **monoclonal antibody** that ***block*** **IL-6 receptor**.

Indications; **RA** and **juvenile idiopathic arthritis**.

- ***Recommendations***; ***Monotherapy*** (***first-line therapy***) or in ***combination*** (*not with other biologic drugs*) with ***other*** **DMARDs** such as **Methotrexate**.
- ***Dose***; - **IV *infusion***; 4-8 mg/kg every 4 weeks.
  - **SC**; <100 kg: 162 mg SC every other week, may by an increase to every week.
    ≥100 kg: 162 mg SC every week.
- ***Pregnancy***; **category C**.
- ***Common side effects***; **Infusion reactions**, ***increased*** **risk of infection**, and ***increased*** **plasma lipids** and ***risk of*** **GI perforation**.

Janus Kinase (JAK) Inhibitors

Tofacitinib (Xeljanz®)#

- **Tofacitinib** is an ***oral inhibitor*** of **Janus kinases** (***first oral biologic***).
- **JAK** is a *human* **tyrosine kinase** essential for ***signaling*** for *certain types* of **cytokines**.

Indications; ***Moderate*** to ***severe*** **active RA**.

- ***Recommendations***; ***second-line treatment*** as **monotherapy** or in **combination** ***with*** **MTX** or ***other*** **non-biologic DMARDs** or ***potent*** **immunosuppressive agents** (**Azathioprine** and **Cyclosporine**).
- ***Pharmacokinetics***;
  - ***Bioavailability***: 74%. - ***Protein Bound***: ~40%
  - ***Metabolism***; CYP3A4 and CYP2C19 (**dosage adjustments** in ***potent*** **inhibitors** or **inducers**).
  - ***Clearance***: ~70% hepatic metabolism and 30% renal excretion.
- ***Dose***; 5 mg orally 2 times a day (*immediate release*) or 11 mg orally once a day (*extended release*).
- ***Dose adjustment***;
  - ***Moderate-severe*** **renal impairment**; Not to exceed 5 mg per day.
  - ***Moderate*** **hepatic impairment**; Not to exceed 5 mg per day.
  - ***Severe*** **hepatic impairment**; Not recommended.
- ***Pregnancy***; **category D**.

** ***Precautions*** or ***Contraindications***;

- **Hemoglobin *concentrations*** must be ***greater than*** **9 g/dL** *before* ***start*** **Tofacitinib**.
- ***Increase*** *risk for* **infections** and **malignancy**.

- ***Monitoring***; **Hemoglobin *concentrations***, **lymphocyte** and **neutrophil** *counts* ***should be*** **checked *during* treatment**.

Drugs for Osteoarthritis

- **Osteoarthritis** (**OA**) is the ***most common*** **joint disease**.
It is ***characterized by breakdown*** of the **cartilage**, **bony** ***changes*** of the **joints**, ***deterioration*** of **tendons** and **ligaments**, and ***various degrees*** of **inflammation** of the **joint lining** (***synovium***).
- The ***daily stresses applied to*** the **joints**, *especially* the **weight-bearing joints**, ***play*** an ***important role*** in the ***development*** of **osteoarthritis**.
Main symptoms; **stiffness** & **locomotor restriction**.
- **Pharmacological therapy** in **OA** is *targeted at* **relief of pain**; *see* ***pain management*** **topic**
  # For ***mild*** or ***moderate pain***, **topical analgesics** or **Paracetamol** ***up to*** **4 gm/day** (**Panadol Joint**®), **NSAIDs** *may be useful*.
  - ***Low-dose*** **opioid analgesics** *can be useful* for **patients** who experience ***no*** **pain relief** with **Paracetamol**, **NSAIDs**, **intra-articular glucocorticoid injections** or **topical therapy**.
- ***Other Therapies*** (***not recommended by guidelines***);

Glucosamine and Chondroitin

Glucosamine *and* Chondroitin (Move Free®)# (Osteo Bi-Flex®)# (Genuphil®)# >>

- **Glucosamine** ($C_6H_{13}NO_5$) is an ***amino sugar*** (*amino-saccharide*).
- **Glucosamine**, acting as a ***substrate*** for the **biosynthesis** of **glycosaminoglycan** ***chains***, **aggrecan** and *other* **proteoglycans** of **cartilage**.
- **Chondroitin** is a **Glycosaminoglycan** (**GAG**) *composed of* a chain of ***alternating sugars*** (**N-acetylgalactosamine** and **Glucuronic acid**).
- **Chondroitin** is an ***important structural*** **component** of **cartilage**.
- **MSM** (**Methylsulfonylmethane**) *occurs* ***naturally*** in **certain foods** *provides* a **source** of **sulfur** for the **body** to ***produce*** **amino acids**, **MSM** *reduce* **pain** and **inflammation**.
Exact role of **Glucosamine**, **Chondroitin**, or a ***combination*** of the two products is ***still unclear***.
Dosing *should be* at ***least*** **1,500 mg/day** of **Glucosamine** and **1,200 mg/day** of **Chondroitin**.
Glucosamine and **Chondroitin** are marketed in the **US** as ***dietary supplements*** and ***not approved*** by the **FDA**.

PRECAUTIONS # # # # # # #

Glucosamine *may*; 1) *Increase risk of* **bleeding**.
2) *Increase* **blood pressure**.
3) *Affect* **insulin resistance** and/or **blood sugar** ***levels***.
4) *Increased* **cataract** *risk* or **dry eyes**.
5) *Use cautiously* in *people who* have **asthma**, **kidney disorders**, ***active*** **peptic ulcer disease** and **depression**.

Hyaluronates Injection

Hyaluronic Acid (HA)	Hyaluronate Sodium

- **Hyaluronic Acid** (**HA**) or **Hyaluronate Sodium** are available for ***intra-articular injection*** for treatment of **knee OA**.
Main functions; as a ***tissue lubricant***.
HA injections ***temporarily*** and ***modestly increase*** **viscosity**.
- ***Intra-articular*** **HAs** ***approved by*** the **FDA** for the treatment of **osteoarthritic knee pain**.
- **HA** ***preparations***: *these agents are* ***expensive***;
  # **Hyalgan**® (20 mg sodium hylaronate/2 mL); weekly for 5 injections.
  # **Supartz**® (25 mg sodium hylaronate/2.5 mL); weekly for 5 injections.
  # **Euflexxa**® (20 mg sodium hylaronate/2 mL); weekly for 3 injections.
  # **Synvisc**® (16 mg hylan polymers/ 2 mL); weekly for 3 injections.
  # **Synvisc**®**-One** (48 mg hylan polymers/6 mL); single dose with efficacy up to 26 weeks.
  # **Orthovisc**® (30 mg hyaluronan/2 mL); weekly for 3 injections.
- ***Other uses*** of **HA**;
  # In **Ophthalmic Viscosurgical Device** (**OVD**); is ***viscoelastic solution*** used in **eye surgery**.
  # **Skin care** and **lip augmentation**; ***creams***, ***serums***, ***injections*** (**Restylane**®) and as ***oral supplements***; **increases in skin moisture** and **decrease wrinkles**.

Drugs for Osteoporosis

- **Osteoporosis** is a ***metabolic bone disorder*** *characterized by* ***low*** **bone density**, ***decreasing*** its **strength** and ***resulting in increased*** **risk** *for* **bone fracture**.
- It is the ***most common*** **reason** for a **broken bone** in ***elderly***.
- ***Typically***; ***no symptoms***, ***until*** a **broken bone** ***occurs***.
- **Bone loss** ***increases after*** **menopause** (**postmenopause**) *due to* ***lower levels*** of **Estrogen**.

Non-pharmacological Therapy

Bone-Healthy Lifestyle

- ***Diet***; * **Calcium and Vitamin D**; **Calcium** *and* **Vitamin D**.
  - **Vitamin K**; **Vitamin K** is a cofactor for ***carboxylation*** (*activation*) of proteins, such as **Osteocalcin**, which are involved in **bone formation**.
  - **Dietary Soy**; **Soy Isoflavones** are naturally occurring ***selective*** **estrogen receptor modulators**, with ***potential*** **bone protective** ***effects***.
- ***Avoid Alcohol*** and ***Decrease Caffeine***, ***Sodium*** *and* ***Smoking***.
- ***Carbonated Beverages***; **Phosphorus** intake (*soft drinks such as Cola*): ***reduced*** **bone mineral density (BMD)** and ***increased*** **fracture risk**.
- ***Exercise***; ***decrease*** the **risk of falls** and **fractures**.
- ***Fall Prevention***; **Patients** *should be* ***educated*** on **personal** and **home** ***safety options*** to ***decrease*** **falls**.

Drugs for Osteoporosis

Calcium & Vitamin D Supplementation

Calcium (Osteocare®)# (Marcal®)# (Caldin-C®)# (Calcitron®)# >>>

- ***Commonly used*** **Calcium supplements** include **Calcium Carbonate** & **Calcium Citrate**.
- **Calcium Carbonate** is generally ***less*** **expensive** and has ***better absorption*** *with* **food**.
- **Calcium** ***dietary*** **intake** *needs* to be known to ***calculate*** **correct** ***safe*** **supplemental dose**.
- ***Common side effects***; **Constipation**, **bloating**, **gas**, **stomach upset** and *rare* **kidney stones**.
- ***Common drug interactions***;
  - **Calcium** ***decrease*** **absorption** of **Iron**, **Tetracycline**, **Quinolones**, **Bisphosphonates**, **Phenytoin** and **Levothyroxine**.
  - **Calcium** ***increase*** the **effects** of **Digoxin**.
  - **Calcium** ***induce*** **hypercalcemia** with **Thiazide Diuretics**.
  - **Calcium** ***decrease*** the **effects** of **Calcium Channel Blockers** (**Diltiazem** and **Verapamil**).

Vitamin D Preparations

- **Vitamin D_2** & **Vitamin D_3** are ***not bioequivalent*** & ***should not*** be ***considered interchangeable***.
- **Vitamin D_3** is ***preferred over*** **Vitamin D_2**, because of its ***shorter half-life*** and ***decreased*** **potency** and **toxicity** (*little evidence*).
- ***Both*** **Vitamin D_2** and **Vitamin D_3** need to ***activation*** by ***hepatic metabolism*** to **25 (OH) vitamin D_3** and ***then*** ***renal metabolism*** to **1α,25(OH)$_2$ vitamin D_3** (**Calcitriol**; *the active moiety*).
- ***Common side effects***; **Hypercalcemia**, (weakness, headache, somnolence, nausea, cardiac rhythm disturbance) and **hypercalciuria**.
- ***Common drug interactions***;
  - **Phenytoin**, **Barbiturates**, **Carbamazepine**, **Rifampin** ***increase*** **Vitamin D** ***metabolism***.
  - **Cholestyramine**, **Colestipol**, **Orlistat** and **Mineral oil** ***decrease*** **Vitamin D** ***absorption***.

Ergocalciferol (Drisdol®)# (Sterogyl®)#

- **Ergocalciferol** is an ***inactive form*** of **vitamin D** (**vitamin D_2**).

Indications; ***treatment of*** **hypoparathyroidism, vitamin D resistant rickets** and **familial hypophosphatemia**.

- ***Dose***; - **Vitamin D Resistant Rickets**: 12,000 to 500,000 IU units daily.
  - **Hypoparathyroidism**: 50,000 to 200,000 IU units daily.
  - **Dose for vitamin D deficiency**; 50,000 units (1.25 mg) once to twice weekly for 8–12 weeks; repeat as needed until therapeutic concentrations; occasionally 50,000 units monthly for maintenance.

Sterogyl® 15 "A"; Oral solution 600,000 IU/1.5 ml: (alcohol-based, colorless) Ampoule-vial filled to 1.5 ml, unit pack; in a ***single dose***, ***once*** a **year**.

Sterogyl® 15 "H": Oral and IM injection solution 600,000 IU/1.5 ml (oil-based, light yellow): Ampoule-vial filled to 1.5 ml, unit pack; in a ***single dose***, ***once*** a **year**.

Cholecalciferol (Devarol-S®)# (Vi-De 3®)# (Vidrop®)#

- **Cholecalciferol** is an ***inactive form*** of **vitamin D** (**vitamin D_3**).
- ***Indications***; **Vitamin D deficiency prevention and treatment**.

Dose; 400–1,000 units/day orally ***or*** 100,000–200,000 units IM every 3-6 months to achieve adequate intake.

Alfacalcidol or 1-hydroxycholecalciferol [1α (OH) D_3] (One-Alpha®)#

- **Alfacalcidol** is an ***inactive form*** of **vitamin D** [**1α (OH) D_3**].
- ***Activation***; **Alfacalcidol** need only to ***activation*** by ***hepatic metabolism***.
- ***Indications***; ***Most commonly*** for **Vitamin D deficiency in *patients with* end stage renal disease** (due to impaired renal second hydroxylation step).
- ***Dose***; 0.25-1 µg/day orally ***or*** injection.

Calcitriol or 1,25-dihydroxycholecalciferol [1,25-$(OH)_2$ D_3] (Rocaltrol®)#

- **Calcitriol** is an ***active form*** of **vitamin D** [**1α, 25 $(OH)_2$ D_3**].
- ***Activation***; **Calcitriol *not need activation***.
- ***Indications***; **hypocalcemia, renal osteodystrophy, hypoparathyroidism** and **secondary hyperparathyroidism**.
- ***Dose***; 0.25–0.5 mcg orally ***or*** 1–2 mcg/mL intravenously daily.

Dihydrotachysterol (Hytakerol®)

- **Dihydrotachysterol** (**DHT**) is a ***synthetic vitamin D analog***.
- ***Activation***; ***activated*** in the **liver** that ***does not*** **require renal activation**.
- ***Indications***; **hypocalcemia, hypophosphatemia, rickets, osteomalacia, hypoparathyroidism, renal osteodystrophy** and **osteoporosis**.
- ***Dose***; ***in*** **osteoporosis**; 0.6 mg orally once a day.
- **19-nor-1,25-dihydroxyvitamin D2** (**Paricalcitol**) and **Calcipotriene** or **Calcipotriol** are ***analogs of*** **Calcitriol** are ***approved for*** **treatment** of ***secondary hyperparathyroidism*** in *patients with* **chronic kidney disease**. **Calcipotriene** is ***approved for*** **topical treatment** of **psoriasis**.

Antiresorptive Medications

- ***Antiresorptive***; agents that act by ***slowing*** **bone loss** by ***inhibiting*** the ***function*** of **osteoclasts**.

Bisphosphonates (BPs)

Bisphosphonates are ***potent*** **bone resorption inhibitors** and ***most commonly*** *prescribed* **antiresorptive medications** and ***remain*** **first-line** ***treatment for*** **osteoporosis**.

- **Bisphosphonates** (P-C-P) are ***biological analogues*** of naturally occurring **pyrophosphates** (P-O-P)
- They are ***called*** **bisphosphonates** because they have ***two*** **phosphonate** ***groups***.

Pyrophosphates are byproducts of ATP metabolism but have no biological activity because of the ubiquitous presence of pyrophosphatases

Bisphosphonates are ***used*** to treat **osteoporosis**, **Paget's disease** and ***certain types*** of **cancer** (***such as*** **bone metastasis** and **multiple myeloma**).

Oral and ***intravenous*** formulation of **Bisphosphonate** are ***available***.

Alendronate (Fosamax®)#	**Ibandronate** (Boniva®)#	**Risedronate** (Actonel®)#
Zoledronic acid (Zometa®)#	**Pamidronate** (Aredia®)#	**Clodronate** (Loron®)#
Etidronate (Didronel®)#	**Neridronate** (Nerixia®)#	**Tiludronate** (Skelid®)#

- **Alendronate**, **Neridronate**, **Ibandronate**, **Pamidronate**, **Risedronate** and **Zoledronic acid** have a ***nitrogen group*** and are *called* **nitrogen-containing BPs** (2nd and 3rd generation).
- ***Non*-nitrogen-containing BPs** are **Etidronate**, **Clodronate** & **Tiludronate** (1st generation).

Alendronate, **Ibandronate**, **Risedronate** and **Zoledronate** are the ***most popular first-line*** **bisphosphonate** used in **osteoporosis** and **Paget's**.

Oral BPs; **Alendronate**, **Ibandronate**, **Risedronate**, **Clodronate**, **Etidronate** & **Tiludronate**.

IV BPs; **Ibandronate**, **Zoledronic acid**, **Pamidronate**, **Neridronate** & **Tiludronate**.

Oral **bisphosphonates** are ***dosed on*** a **daily**, **weekly** or **monthly**.

IV **bisphosphonates** are ***dosed on*** **quarterly** (3 months) or **yearly**.

Bisphosphonates have an ***extremely high*** ***affinity*** for **bone tissue**.

Absorption of **oral** **bisphosphonates** is ***very*** ***poor*** (<1-10%), **food** and ***other*** **medications** (*such as* Calcium & Iron) *significantly* ***decrease absorption***.

20-80% of ***absorbed rapidly*** ***uptake*** by **bone** and the **remainder** ***rapidly excreted*** in the **urine**.

Bisphosphonates ***once bound*** to **bone**, they are ***cleared over*** a *period of* **hours** to **years**.

Bisphosphonates ***decrease*** **osteoclastic bone resorption** ***through*** an ***increase*** in **osteoclastic apoptosis** (*programmed cell death*) and ***decrease*** **osteoclast activity**.

Side effects;

- **Oral bisphosphonates**;
  - # **Stomach upset**, **inflammation** and **erosions** ***of the*** **esophagus** (main problem of oral N-containing preparations; *see precautions and patient counselling*).
  - # **Musculoskeletal pain**.
- **IV bisphosphonates**;
  - # **Fever** & **flu-like symptoms** (*acute inflammatory response*) after the ***first*** **infusion**.
  - # **Osteonecrosis** ***of the*** **jaw** (**ONJ**) *especially with higher doses for treatment cancer*.

Bisphosphonates PRECAUTIONS

1) ***Before starting bisphosphonates***; ***evaluation for*** **hypocalcemia, vitamin D deficiency** and **renal impairment**; hypocalcemia and/or vitamin D deficiency must be corrected.

2) ***Each*** **oral dose** ***should be*** taken ***alone*** on an ***empty stomach*** [*morning*] with ***at least*** **240 mL** of **tap water** (not coffee, juice, mineral water or milk) [enteric-coated delayed-release formulation (weekly) needs to be taken with only ~100mL] ***at least*** **30** (60 for **Ibandronate**) **minutes** ***before*** **consuming** ***any*** **food, supplements** (**Calcium**) or **medications** [*because bioavailability is very poor and to minimize GI side effects*].

3) **The patient** ***should be remain*** **upright** (*sitting or standing*) for ***at least*** **30 minutes** (60 for **Ibandronate**) [*to minimize esophagus ulceration*].

4) ***If missed dose***; - ***Weekly dose***; can take it the ***next day***, if ***more than*** **1 day** the ***dose is skipped*** *until* the **next week**.

- ***Monthly dose***; it can be ***taken*** up to **7 days** ***before*** the **next administration**.

5) **Patient** ***should*** **take** **Calcium** and **Vitamin D** (**Calcium** ***should not take at the same time***; at least one hour after bisphosphonates); **Fosamax® Plus** & **Fosavance®**; **Alendronate** + **Cholecalciferol**.

6) ***Should not*** be **given** to ***patients with*** **active upper GI disease**.

7) ***Should*** be ***discontinued*** in ***patients who*** **develop** ***any*** **symptoms** of **esophagitis**.

8) ***Delay*** **bisphosphonate therapy** in **dental** ***implant*** or ***extraction*** for a ***few*** **months** ***until*** **healing** of the **jaw** is ***complete***.

9) ***Once-yearly administration of*** **Zoledronic acid** ***should be infused over at least*** **15 minutes** with a **pump** [**Acetaminophen** or **ibuprofen** can be given to ***decrease*** **acute phase reactions**].

** **Dose** ** **For Osteoporosis** **

- **Alendronate**; *For prevention*; 5 mg daily or 35 mg weekly
  - *For treatment*; 10 mg daily or 70 mg tablet (**Fosavance®**; 70 mg tablet + vitamin D 2,800 or 5,600 units), or 75 mL liquid weekly.
- **Risedronate**; 5 mg daily, 35 mg weekly, 75 mg for 2 days monthly, 150 mg monthly
- **Ibandronate**; 150 mg monthly, 3 mg intravenous quarterly (every 3 months).
- **Zoledronic acid**; *For Treatment*; 5 mg intravenous infusion yearly.
  - *For Prevention*; 5 mg intravenous infusion every 2 year.

Selective Estrogen Receptor Modulators (SERMs)

- **Selective estrogen receptor modulators** (**SERMs**) are a **class of drugs** that *act on* the **estrogen receptor**, *produce* **estrogenic** and **anti-estrogenic effects** ***depending on*** the **specific tissue** (**mixed estrogen agonist/antagonist**; **EAA**).
- **SERMs** are considered to provide the ***beneficial effects*** of **Estrogen** ***without*** the **potentially adverse** ***outcomes***.
- **SERMs** are ***used dependent*** on their **pattern of action** in **various tissues**:

Femarelle® is a ***dietary supplement*** that may act as a **SERM**, it can ***reduce*** the **risk** for **osteoporosis**.

Raloxifene (Evista®)#

Raloxifene is a ***selective*** **estrogen receptor modulator** (**SERM**) ***approved for*** the ***prevention*** and ***treatment*** of **osteoporosis in postmenopausal women**.

It has ***estrogen-like effects*** on **bone** and ***estrogen antagonist effects*** on **breast** and **endometrium**.

- It is ***FDA-approved*** for ***reduction*** in **risk** of **invasive breast cancer**.
- ***Supplemental*** **Calcium** and **Vitamin D** ***should be*** **added**.
- **Raloxifene** causes some ***+ve*** **lipid effects**; ***reduces*** **levels** of **total cholesterol** and **LDL**.
- ***Dose***; 60 mg orally once a day.
- ***Common side effects***; **hot flashes** and **leg cramps**.
- ***FDA black box warning***; ***risk*** of ***venous thromboembolism*** and **death** *due to* **stroke**.

Pregnancy; **Raloxifene** is a **teratogenic drug** (**Category X**).

- ***Contradictions***; **lactating women** or **pregnant women** and in **women** with ***active*** or ***past history*** of **venous thromboembolic events**.

Bazedoxifene (Viviant®)#/Conjugated Estrogens (Premarin®)# OR Bazedoxifene/Conjugated Estrogens (Duavee®)#

- **Bazedoxifene** is a ***3rd generation*** ***selective*** **estrogen receptor modulator**; *by Pfizer*.

In 2013, **Duavee®** (**Bazedoxifene/Conjugated Estrogens**) *approval for* ***prevention*** (*not treatment*) of **postmenopausal osteoporosis**.

- **Conjugated Estrogens**; are ***blended equine*** **estrogens**, which may include estrone sulfate, equilin sulfate and equilenin sulfate.

Conjugated Estrogens are ***added*** to;
  - ***Reduced risk*** of **endometrial hyperplasia**.
  - ***Reduced*** **vasomotor symptoms** (**hot flashes**) of ***menopause***.

- ***Dose***; **Conjugated Estrogens** 0.45 mg and **Bazedoxifene** 20 mg orally ***once*** a day.
- ***FDA black box warning***; ***risk*** of; ***venous thromboembolism***, **endometrial/breast cancer** and **probable dementia**.

Pregnancy; **Category X**.

Calcitonin Hormone

Calcitonin (Miacalcic®)# (Miacalcin®)# (Fortical®)#

- **Calcitonin** is an ***endogenous hormone released from*** the **thyroid gland** when ***serum*** **calcium** is ***elevated***, ***opposing*** the **effects** of **parathyroid hormone** (**PTH**).
- It is ***produced*** either by **recombinant DNA technology** or by **chemical peptide synthesis** of **Salmon Calcitonin** (*Salmon fish*).
- **Calcitonin-Salmon**; is ***more potent*** and ***longer lasting*** than **Mammalian Calcitonin**.

Indications; - **Postmenopausal Osteoporosis** (> 5 years of postmenopause); **intranasal** ***preferred than*** **parenteral**.
- ***Acute management*** **hypercalcemia** (*only IM or SC*).
- ***Symptomatic*** **Paget's disease** (*only IM or SC*).

- ***Because*** **efficacy** is ***less than*** the ***other*** **antiresorptive therapies** (*such as* **bisphosphonates**), **Calcitonin** is *reserved as* ***third-line treatment***.
- ***Dose***; In **Postmenopausal Osteoporosis**; - ***SC/IM***; 100 IU every other day.
  - ***Nasal Spray***: 1 spray (200 IU) daily.
- ***N.B.***; In **osteoporosis** ***ensure*** **adequate Calcium** and **Vitamin D intake**.
- ***Efficacy***; ***Only*** **vertebral fractures** ***decrease*** with ***intranasal*** **calcitonin therapy** (not affect hip).
- ***Pregnancy***; **Category C**.
- ***Warning***; - **Hypersensitivity reactions** (*anaphylaxis*).
  - **Nasal adverse reactions** (*rhinitis*).
  - **Malignancy**.
  - **Risk of hypocalcemia**.

Monoclonal Antibody

Denosumab (Prolia®)# (Xgeva®)#

- **Denosumab** is ***a monoclonal antibody*** with ***affinity*** for **nuclear factor-kappa ligand** (**RANKL**).

Indications; - **Prolia®**; **Postmenopausal osteoporosis** (*with high risk of fracture*) *and* **bone loss** (*due to certain medications*).
- **Xgeva®**; **Hypercalcemia** of **malignancy** and **bone metastases**.

- ***Off-label***; **bone destruction** ***caused by*** **rheumatoid arthritis**.
- ***Dose***; 60 mg SC as a single dose, once every 6 months.
- ***N.B.***; ***Ensure*** **adequate Calcium** and **Vitamin D intake**.
- ***Most common side effects***; **joint** and **muscle pain**, ***increased*** **risk of infections** (*cellulitis*) and **hypocalcemia**, **hypersensitivity allergy reactions**, **osteonecrosis** *of the* **jaw** (**ONJ**) and **atypical hip fractures**.
- ***Pregnancy***; **Category D**.
- ***Contraindications***; ***Pre-existing*** **hypercalcemia**.
- **Romosozumab** is an ***anti-sclerostin monoclonal antibody*** in development for the treatment of **osteoporosis in postmenopausal women** at ***increased*** **risk of fracture** (*not approved*; 5/2017).

Hormone Replacement Therapy (HRT)

- *Although* **Estrogens** are ***FDA indicated*** for ***prevention*** of **osteoporosis**, they should only be used ***short-term***, because adverse effects associated with estrogen therapy (e.g., risks for breast cancer, myocardial infarction, stroke, and venous thromboembolic events).
- **Hormone replacement therapy** (**HRT**) [**Estrogen** ***with*** or ***without*** **Progestogen**] is ***not currently*** **recommended** for the ***treatment*** of **osteoporosis**.

Anabolic Therapy

Parathyroid Hormone (PTH)

Teriparatide (Forteo®)#

Teriparatide is a *recombinant form* of human parathyroid hormone (PTH).
- It is the *only* available anabolic agent (*bone growing*) for the *treatment of* osteoporosis.
- *Mechanism of action*;
  - *Endogenous* PTH *regulate* Calcium and Phosphate *metabolism* in bone and kidney.
  - PTH *increase* serum Calcium by *increasing* bone resorption (chronically elevated PTH will deplete bone stores).
  - *However*, *intermittent* exposure to PTH (once-daily injections of Teriparatide) will *activate* osteoblasts *more than* osteoclasts, *stimulating* new bone formation *leading to increased* bone mineral density.

Teriparatide *increases* bone formation, bone remodeling rate, osteoblast number *and* activity.

Teriparatide is the *first* drug that *stimulates* bone formation (other agents inhibit bone resorption).

Indications; - Osteoporosis in men (primary or hypogonadal osteoporosis); *with high risk for fracture.*
- Osteoporosis in postmenopausal women: *with high risk for fracture.*
- Glucocorticoid-induced osteoporosis; *with high risk for fracture.*

- *N.B.*; Teriparatide *should be reserved for* patients at *high risk of fractures* and those who have *failed* or *cannot* tolerate *other* osteoporosis therapies.
- *Off-label*; Teriparatide also *accelerates* fracture healing.
- *N.B.*; *Ensure* adequate Calcium and Vitamin D intake (before treatment, levels of serum Calcium, PTH, and 25(OH) D need to be *monitored*).

Dose; SC injection 20 mcg once a day in the thigh or abdomen.
- *Pregnancy*; Category C.
- *Contraindications*; - Teriparatide administration *not recommended more than* 2 years (safety and efficacy not been evaluated).
  - *Pre-existing* hypercalcemia.
  - *Severe* renal impairment.
  - Metabolic bone diseases *other than* primary osteoporosis (such as hyperparathyroidism and Paget's disease).

FDA black box warning; Teriparatide has been *associated with* an *increased risk* of osteosarcoma (cancerous tumor in a bone) in rats.

Other Agents

Strontium Ranelate (Protelos®)#

- Strontium Ranelate is composed of Ranelic acid and Strontium.
- It *increases* collagen and non-collagenic proteins *synthesis* by *mature* osteoblast enriched cells.
- The effects on bone formation were *confirmed* by *enhanced pre*-osteoblastic cells replication.
- Strontium Ranelate is *not approved* by the US FDA, *but* in the United Kingdom is *prescribed*.
- *Should be* taken 2 hours *before* food or other agents.

Cardiovascular System (CVS)

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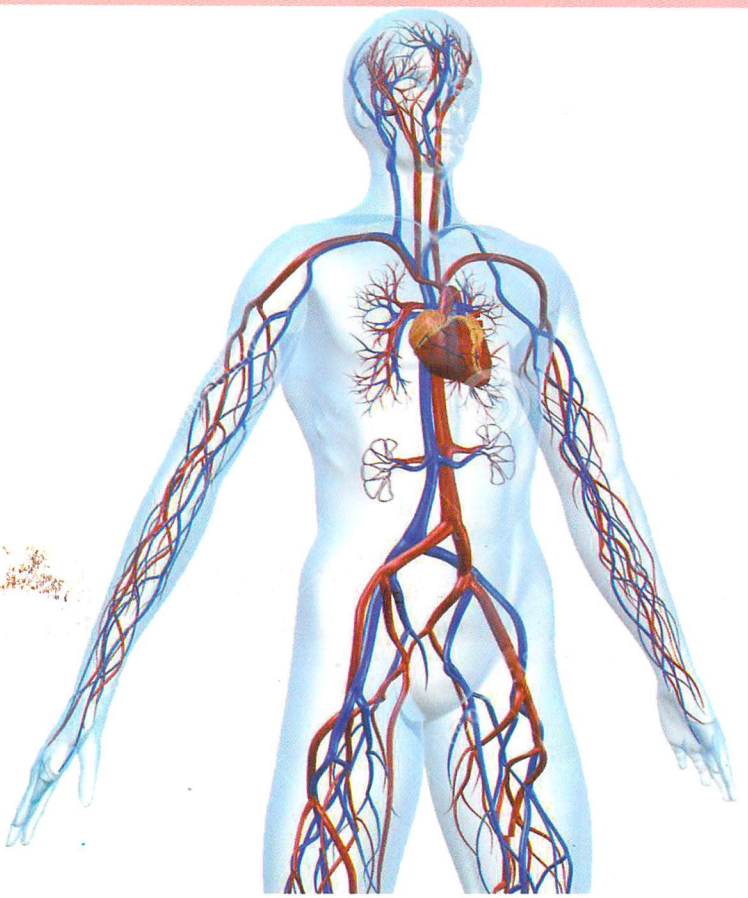


Hypertension

➢ Normal Resting Blood Pressure by Age:-

Blood Pressure Value	Male Age (year)			Female Age (year)		
	10-15	20-30	50-60	10-15	20-30	50-60
Systolic blood pressure SBP (mmHg)	100	120	134	84	120	130
Diastolic blood pressure DBP (mmHg)	60	80	84	40	74	84
Mean arterial pressure MAP (mmHg)	73	93	97	55	88	92

BP = Cardiac Output (CO) X Peripheral Vascular Resistance (PVR)

- **Cardiac Output (CO)**: **CO** = Stroke Volume (**SV**) **X** Heart Rate (**HR**)
- **Stroke Volume (SV)**: is the volume of blood pumped from the left ventricle of the heart per beat.
- **Heart Rate (HR)**: is the speed of the heartbeat measured by the number of poundings of the heart per unit of time (typically beats per minute).
  - ***Increase*** **CO** or **PVR**, or **both** ⇨ ***Increase*** BP.
  - ***Decrease*** **CO** or **PVR**, or **both** ⇨ ***Decrease*** BP.

➢ Classification of Hypertension by American Heart Association:-

Blood Pressure Category	Systolic (mmHg)		Diastolic (mmHg)	Follow-up and Notes
Normal	< 120	and	< 80	- Yearly checks. - Healthy lifestyle choice.
Elevate Blood Pressure	120-129	and	< 80	- Reassessed in 3-6 months. - Healthy lifestyle modifications.
Stage 1	130-139	or	80-89	- Reassessed in 3-6 months. - Monthly follow-up until BP is controlled. - 10-year heart disease & stroke risk assessment. - Healthy lifestyle modifications.
Stage 2	≥ 140	or	≥ 90	- Monthly follow-up until BP is controlled. - Healthy lifestyle modifications. - 2 different classes of medicine.
Hypertensive Crisis	> 180	and/or	> 120	- Emergency care needed

R; **American Heart Association New Guidelines** (Published; Nov, 13, 2017).

➢ Diagnosis of Hypertension:-

- **NO** ***Smoking***, **NO** ***Exercise*** and **NO** ***Coffee***; **30 minutes** ***before*** **BP** is ***taken***.
- **Patient** ***should be*** **seated quietly** *in* **chair** *for* ***at least*** **5 minutes** (**NO** ***taking***).
- **Reading** ***should be*** based on the **average of two or more readings taken at each** *of* **two** *or* **more clinical encounters**.

➢ Uncontrolled Hypertension Effects on the Body:-

Arteries Damage;
- Artery walls thick and stiff (**arteriosclerosis**).
- ***Cause***; angina (chest pain), heart attack, heart failure, kidney failure, stroke, blocked arteries in legs or arms (peripheral artery disease) and eye damage.

Heart Damage;
- Uncontrolled high blood pressure can damage the heart in a number of ways, such as: **coronary artery disease**, **enlarged left heart** (left ventricular hypertrophy) and **heart failure** (heart muscle weakness and work less efficiently).

Kidneys Damage;
- Uncontrolled high blood pressure can injure renal blood vessels and leading **nephropathy**
- ***Cause***, weakens and damages the artery wall, lead to kidney failure.
- Diabetes in addition to high blood pressure can worsen the damage.

Eye Damage;
- *Cause*; **Hypertensive Retinopathy**:
  - Damage in the arterial and arteriolar circulation in response to the high blood pressure.

Brain Damage;
- **Stroke**; due to damaging and weakening brain blood vessels.
- **Dementia;** due to narrowing and blockage of the arteries that supply blood to the brain.

➢ Classification of Hypertension Defined by Causes:-

- **Primary** (**Essential** or **Idiopathic**) **Hypertension**: Majority of cases about 90%
  - No specific medical causes (no identifiable causes).
  - Unknown etiology but multiple factors may contribute to the development of primary hypertension including;
    - Smoking, obesity, stressful lifestyle, high dietary intake of sodium, family history and alcohol intake.
    - Overactive of renin-angiotensin system or sympathetic nervous system.
    - Deficiency in the local synthesis of vasodilating substances (NO, bradykinin and prostacyclin) or excess vasoconstricting substances (angiotensin II and endothelin).
    - Insulin resistance, hyperinsulinemia and obesity, also linked with renin-angiotensin system.
    - Vitamin D deficiency may leads to an increase in renin secretion.
- **Secondary Hypertension**: Few cases about 10%.
  - Most of these are caused by ↘
    - Chronic kidney disease or renovascular disease.
    - Primary aldosteronism (Conn's syndrome) & hypercortisolism (Cushing's syndrome).
    - Pheochromocytoma and hyperthyroidism.
    - Drugs may increase BP include; Corticosteroids, Estrogens, NSAIDs & Amphetamines.

➢ Treatments of Hypertension:-

Lifestyle Modification (Non-pharmacologic treatments)	Medications (Antihypertensive drugs)
- **Dietary Approaches to Stop Hypertension (DASH) eating plan**; *- BP reduced by 8–14 mm Hg.* - **Dietary sodium** (salts) **restriction**: *- BP reduced by 2–8 mm Hg.* - **Weight loss**; Normal (BMI 18.5–24.9 kg/m2) *- BP reduced by 5–20 mm Hg per 10-kg loss.* - **Regular aerobic physical activity**: *- BP reduced by 2–9 mm Hg.* - **Moderate alcohol consumption**: *- BP reduced by 2–4 mm Hg.* - **Smoking cessation**. - **Reduction of environmental stressors**.	- Diuretics. - β-blockers (BBs). - ACE Inhibitors (ACEIs). - Angiotensin Receptor Blockers (ARBs). - Direct Renin Inhibitors. - α-blockers. - Calcium Channel Blockers (CCBs). - Centrally Acting Sympathetic Inhibitors. - Peripherally Acting Sympathetic Inhibitors - Ganglionic Blockers. - Vasodilators. - Natural Antihypertensive Agents.

* **Lifestyle modification *alone*** are **effective for most patients with prehypertension, *but* is insufficient alone for patients with hypertension.**

Diuretics

Thiazide Diuretics (Low Ceiling)

Hydrochlorothiazide (Esidrix®)# (Hydretic®)# | **Chlorthalidone** (Thalitone®)

Thiazide diuretics are ***not effective*** in **patients with inadequate kidney function** (estimated glomerular filtration rate less than 30 mL/min/m^2). **Loop diuretics** may be required in these patients.

- ***Dose***; **Hydrochlorothiazide**; 25-100 mg/day (single). **Chlorthalidone**; 25-50 mg/day (single).

Uses; **1) Mild and moderate hypertension.** **2) Congestive heart failure (CHF).** **3) Nephrolithiasis (Idiopathic hypercalciuria).** **4) Nephrogenic diabetes insipidus.**

Side effects; **Hypokalemia**, **metabolic alkalosis**, **hypercalcaemia**, **hyperuricemia**, **hyperlipidemia**, **hyperglycemia**, **hyponatremia**, **hypomagnesaemia**, **hypersensitivity**.

Contraindications; **Digitalis toxicity**, **hepatic cirrhosis** (overzealous use), **renal failure**, **sulfonamide allergy**, **gout** and **diabetes mellitus**.

Drug interactions; **Lithium**, **Digitalis** and **NSAIDs**.

Thiazide-Like Diuretics (Thiazide Analogues)

Indapamide (Natrilix® SR)# (Hypotense®)

Indapamide is the ***first*** of a ***new class*** of '**antihypertensive/diuretics**'.

It have a **unique mechanism of action**; act by combining **diuretic effects** ***with*** a **direct vasodilatation** (Ca^{2+} channels blocker) **effect**.

It ***used*** in **hypertension** and **edema** *due to* **congestive heart failure**.

- ***Dose***; 2.5-10 mg/day (*single dose*).
- The drug produces toxicity similar to that of the thiazide diuretics.

Clopamide (Hypoten®)# | **Xipamide** (Epitens®) | **Metolazone** (Zaroxolyn®)#

Clopamide, **Xipamide** and **Metolazone** are a **thiazide-like diuretic** and works in *similar way* as the **thiazide diuretics**.

Loop Diuretics (High Ceiling)

Loop diuretics are the ***most efficacious*** **diuretic agents currently available**.

Loop diuretics are ***more effective*** in **patients with impaired kidney function**.

Furosemide (Lasix®)# | **Torsemide** (Examide®)# (Torseretic®)#

Bumetanide (Burinex®)# (Edemex®) | **Ethacrynic acid** (Edecrin®)#

Furosemide, **Torsemide**, **Bumetanide** are ***sulfonamide*** **loop diuretics**.

Ethacrynic acid, ***not a sulfonamide*** **diuretics**.

- ***Doses***;

Drug	Total daily dose	Relative potency
Furosemide	20-80 mg	1
Torsemide	5-20 mg	3
Bumetanide	0.5-2 mg	40
Ethacrynic acid	50-200 mg	0.7

Uses; **1) Edema.** **2) Hypertension.** **3) Hyperkalemia.** **4) Oliguria** (< 400 ml urine/day); ***only*** **high dose**; **Lasix 500 mg** tab. or **Lasix 250 mg** amp.

Side effects; **Hypokalemia**, **metabolic alkalosis**, **ototoxicity**, **hyperuricemia**, **hypomagnesaemia**, **hyponatremia**, ***severe*** **dehydration**, **hyperlipidemia**, **hyperglycemia** and **hypersensitivity**.

Contraindications; **Digitalis toxicity**, **hepatic cirrhosis** (overzealous use), **sulfonamide allergy** and **Gout**.

Drug interactions; **Aminoglycosides**, **Lithium**, **Digitalis**, **Warfarin** and **NSAIDs**.

Potassium (K^+) Sparing Diuretics

- **Potassium-sparing diuretics** ***prevent*** **K^+ secretion** by antagonizing the effects of aldosterone in collecting tubules (aldosterone antagonists) ***or*** by inhibition of Na^+ influx through ion channels in the luminal membrane (non-aldosterone antagonists).

Aldosterone Antagonists

Spironolactone (Aldactone®)#	**Eplerenone** (Eplorefix®)#

- **Spironolactone** is a ***synthetic*** **steroid** that acts as a ***competitive*** **antagonist** to **aldosterone** at **mineralocorticoid receptors**, it has a slow ***onset of action*** *requiring* **several days** before ***full*** **therapeutic effect** is achieved.
- **Eplerenone** is a **spironolactone** ***analogue*** with ***much greater*** **selectivity** for the **mineralocorticoid receptors**.
- **Eplerenone** has a ***several*** **hundred-fold** ***less active*** on **androgen** and **progesterone** ***receptors*** *than* **Spironolactone**, therefore, **Eplerenone** has considerably ***fewer*** **adverse effects**.

Uses; **Spironolactone**;

- **Primary hyperaldosteronism** (**Conn's syndrome**):
  - ***Usual adult dose***; Initial dose: 100 mg orally once a day. This dosage may be divided into two daily doses, and increased as tolerated every two to three days to a maximum recommended total daily dose of 400 mg.
- **Edema**; **Congestive heart failure (CHF)**, **Cirrhosis** or **Nephrotic syndrome**:
  - ***Usual adult dose for CHF***; 25 mg/day orally.

Essential hypertension; alone *or* in ***combination*** with **thiazide** or **loop diuretics**!!

1) ***Synergistic*** **diuretic effect**. 2) ***Correct*** **hypokalemia**.

Spironolactone 25 or **50 mg** + **HTZ 25** or **50 mg** (**Aldactazide®**)

Spironolactone 50 or **100 mg** + **Furosemide 20** or **50 mg** (**Lasilactone®**)

- ***Usual adult dose for HTN***; 25 to 200 mg/day orally in 1 or 2 divided doses.

- **Hypokalemia**; ***Usual adult dose***; 25 to 200 mg/day orally in 1 or 2 divided doses.
- **Antiandrogen**; **Hirsutism**, **acne** (in women) & **androgenic alopecia**.
  - ***Usual adult dose for Hirsutism***; 50 to 200 mg/day orally in 1 or 2 divided doses.

Side effects; - **Hyperkalemia** and **metabolic acidosis**.

- **Endocrine abnormalities**; **Gynecomastia** and **Impotence**; all have been reported ***only*** with **Spironolactone**.

Contraindications; **anuria** and **renal insufficiency** and **hyperkalemia**.

- ***Drug interactions***; **Other K^+-sparing diuretics**, **β-blockers**, **NSAIDs**, **ACEIs**, **ARBs**, **Aliskiren**, **K^+ supplements** and **diet rich in K^+**.

- **Diuretics** are ***not*** **part** of the ***standard*** **treatment** for **gestational hypertension** and **edema**. *Their application* is ***limited*** to **special indications**.

Hydrochlorothiazide is the ***drug of choice*** (**Category B**).

Furosemide *may be* **used** to ***manage*** **heart/kidney failure** (**Category C**).

Spironolactone *may be* **used** (**Category C**), it may showed ***feminization*** of **male fetuses** or **endocrine** ***dysfunction*** in *both* **male** and **female**.

Non-aldosterone Antagonists (Epithelial sodium channel blockers)

Amiloride (Midamor®)# | **Triamterene** (Dyrenium®)

- **Amiloride** & **Triamterene** are direct inhibitors of Na^+ influx in cortical collecting tubule

Used as **adjunctive treatment** with **thiazide diuretics** or **loop diuretics** in **congestive heart failure** or **hypertension** to;

1) *Synergistic* **diuretic effect**. 2) *Correct* **hypokalemia**.

Amiloride 5 mg + **Hydrochlorothiazide** 50 mg (**Moduretic®**)

Triamterene 37.5 mg + **Hydrochlorothiazide** 25 mg (**Dyazide®**)

- *Side effects*; - **Hyperkalemia** and **metabolic acidosis**.
  - **Triamterene** may cause **kidney stones** (*due to slightly soluble in urine*).
- *Drug interactions*; **Other K^+-sparing diuretics**, **β-blockers**, **NSAIDs**, **ACEIs**, **ARBs**, **Aliskiren**, **K^+ supplements** and **diet rich in K^+**.
  - **Triamterene** *with* **Indomethacin** has been reported to cause **acute renal failure**.

Carbonic Anhydrase Inhibitors

- By ***blocking*** **carbonic anhydrase** ⇨ ↓ **$NaHCO_3$** *reabsorption* (block Na/H^+ exchange) & cause **diuresis**. **Carbonic anhydrase inhibitors** are ***now*** **rarely used as diuretics**.
- *Pharmacodynamics*; - **Kidney**; weak self-limiting diuretic.
  - **Eye**; ↓ synthesis of aqueous humour (↓ IOP).
  - **CNS**; antiepileptic effects & ↑ ventilation.

Acetazolamide (Diamox®)# | **Methazolamide** (Neptazane®)

Dichlorphenamide (Daranide®) | **Dorzolamide** (Trusopt®)#

Brinzolamide (Azopt®)#

Uses; - **Diuretics** (***but*** **rarely used as diuretics**).
  - **Glaucoma**; **Acetazolamide** ***dose*** in **open angle** (**orally** or **IV**: 250 mg 1 to 4 times a day) and **close angle** (250 to 500 mg **IV**, may repeat in 2 to 4 hours to a maximum of 1 gram/day).

Methazolamide ***dose*** in open and closed; 50 to 100 mg orally 2 to 3 times daily.

Dichlorphenamide ***dose***; ***initial***; 100mg 2 times daily, ***maintenance***; 25-50mg 1 to 3 times daily.

Dorzolamide (Trusopt 2%) & **Brinzolamide** (Azopt 1%) ***dose***; 1 drop 3 times daily.

  - **Urinary alkalinization and metabolic alkalosis**.
  - **Acute mountain sickness** (**Altitude sickness**); due to ↑ ventilation.
  - **Adjuvants in the treatment of epilepsy**.
- *Side effects*; **Hyperchloremic metabolic acidosis**, **hypokalemia** & **hypersensitivity**.
  - **Phosphaturia** and **hypercalciuria**; *due to* alkalinization of urine.
  - *CNS*; **drowsiness** and **paresthesia**.

Osmotic Diuretics

Mannitol (Osmitrol®)

- **Mannitol** is classified as a **sugar alcohol**, which is derived from a sugar (mannose) by reduction. Other sugar alcohols include **xylitol** and **sorbitol**. **Mannitol** and **sorbitol** are ***isomers***.
- *Pharmacokinetics*; Mannitol is poorly absorbed by the GIT, when administered orally, it cause osmotic diarrhea rather than diuresis. For systemic effect, mannitol must be given IV.
- *Uses*; **Mannitol** is used clinically in **osmotherapy**;
  - ***Prevention*** and/or ***treatment*** of the **oliguric phase of acute renal failure**.
  - ***Reduction*** of **intracranial pressure** (**ICP**) and ***treatment*** of **cerebral edema**.
  - ***Reduction*** of elevated **intraocular pressure** (**IOP**); when cannot be lowered by other means.
  - ***Promotion*** of **urinary excretion of toxins**.

Antihypertensive Drugs

1) β-Blocker

All **β-blockers** are useful for ***lowering*** **blood pressure** in ***mild*** **to** ***moderate*** **hypertension**.

In ***severe*** **hypertension**, β-blockers are especially useful in ***preventing*** the **reflex tachycardia** that often results from ***treatment with*** **direct vasodilators**.

β-blockers have been shown to ***reduce*** **mortality** ***after*** a **myocardial infarction** and some also ***reduce*** **mortality in patients with heart failure**.

β-blockers precautions; # # # # # # # # **PATIENT COUNSELLING** # # # # # # #

1) **β-blockers** ***must be*** **tapered off gradually**; ***Long-term*** use of **β-blocker** ⇨ ***up-regulation*** of the **β-receptors**. ***Sudden stop*** ⇨ ***increased*** **receptors sensitivity** and can ***worsen*** **angina** or **hypertension**.

2) ***Non-selective β-blockers*** ***used with caution*** in **insulin-dependent diabetic patients** (***Mask*** **hypoglycemia symptoms**).

3) ***Non-selective β-blockers***, are ***contraindicated*** in patients with **COPD** or **asthma**.

4) **β-blocker** ***not used*** with **non-dihydropyridines** Ca^{2+} **channel blockers** (**Verapamil** and **Diltiazem**) ***to avoid*** **heart block**.

5) **Carvedilol** > **Metoprolol Succinate** > **Bisoprolol** are ***only*** **β-blockers** ***may be used*** in **CHF**.

Propranolol (Inderal®)#	**Nadolol** (Corgard®)#

Propranolol and **Nadolol** are a ***non-selective*** **β-blocker**

Nadolol is ***more potent*** than **Propranolol**.

- **Nadolol** has a ***very long*** **duration of action** with ***low*** **lipid solubility** than **Propranolol**.
- ***Doses***;
  - **Propranolol**: (orally) ***initial***; 80 mg/day. ***Maintenance***; 120-240 mg/day (↑ if needed).
  - **Nadolol**: (orally) ***initial***; 40 mg/day. ***Maintenance***; 40-80 mg/day (↑ if needed)
  - **Propranolol** ***other uses*** (*non-cardio*); **hyperthyroidism, migraine** ***prophylaxis*** & **anxiety**.

Atenolol (Tenormin®)# (Ateno®)	**Bisoprolol** (Concor®)# (Bistol®)
Metoprolol (Lopressor®)#	**Nebivolol** (Nebilet®)# (Nevilob®)
Esmolol (Brevibloc®)#	

They are ***selective*** **β_1-blockers** (***cardioselective***); be ***advantageous*** in **treating hypertensive patients** who also ***suffer from*** **asthma, diabetes** or **peripheral vascular disease**.

Carvedilol > **Metoprolol Succinate** > **Bisoprolol** are ***only*** **β-blockers** ***used*** in **Congestive Heart Failure (CHF)**.

Nebivolol ***induce*** *releases of* **nitric oxide** from **endothelial cells** and causes **vasodilation**.

Esmolol is an ***ultra-short-acting***, **half-life** (***about*** **10 minutes**). It is ***only*** ***available*** **IV** & it is ***used*** *during* **surgery** or **diagnostic procedures**, *sometimes* for **emergency care**.

- ***Doses***;
  - **Metoprolol**: (orally) ***initial***; 100 mg/day. ***Maintenance***; 100-450 mg/day.
  - **Atenolol**: (orally) 50 mg once daily, ***may be increased*** to 100 mg once daily.
  - **Esmolol**: (IV) ***initial***; 500 mcg/kg/min over 1 min, ***Maintenance***; 50 mcg/kg/min for 4 min.
  - **Bisoprolol**: (orally) ***initial***; 5 mg once daily. ***Maintenance***; 5 to 20 mg once daily.
  - **Nebivolol**: (orally) ***initial***; 5 mg once daily. ***Maintenance***: > 40 mg once daily.

Acebutolol (Sectral®)	Pindolol (Visken®)	Celiprolol (Selectol®)
Oxprenolol (Trasicor®)	Penbutolol (Levatol®)	

They are **β-blocker** with ***some*** **intrinsic sympathomimetic activity** (**ISA**), **They lower blood pressure** by ***decreasing*** **vascular resistance** and ***depress*** **cardiac output** or **heart rate** less than other β-blockers, ***and this may be particularly beneficial for*** **patients** with **bradyarrhythmias** or **peripheral vascular disease**.

- ***Doses***;
  - **Acebutolol**: (orally) ***initial***: 400 mg once or 200 mg twice. ***Maintenance***: 400 - 800 mg/day.
  - **Pindolol**: (orally) ***initial***: 5 mg twice daily. ***Maintenance***: 10 to 60 mg/day.
  - **Celiprolol**: (orally) ***initial***: 200 mg once daily. ***Maintenance***: 400 mg/day.
  - **Oxprenolol**: (orally) 80-160 mg a day, 2 to 3 doses. ***Maximum daily*** is 320 mg.
  - **Penbutolol**: (orally) ***initial***: 20 mg once daily. ***Maintenance***: 20 to 40 mg once daily.

Labetalol (Trandate®)	Carvedilol (Dilatrend®)

Labetalol and **Carvedilol** are a ***non-selective*** **β-blocker** and ***selective*** **α_1-blocker**.

Labetalol used in treatment of ***chronic*** or ***acute*** **hypertension** *of* ***pheochromocytoma*** **and** ***hypertensive crisis***.

- **Carvedilol** *reduces* **mortality** in patients with **heart failure** (***protective effect***) and is therefore particularly ***useful*** in patients with ***both*** **heart failure** and **hypertension**.

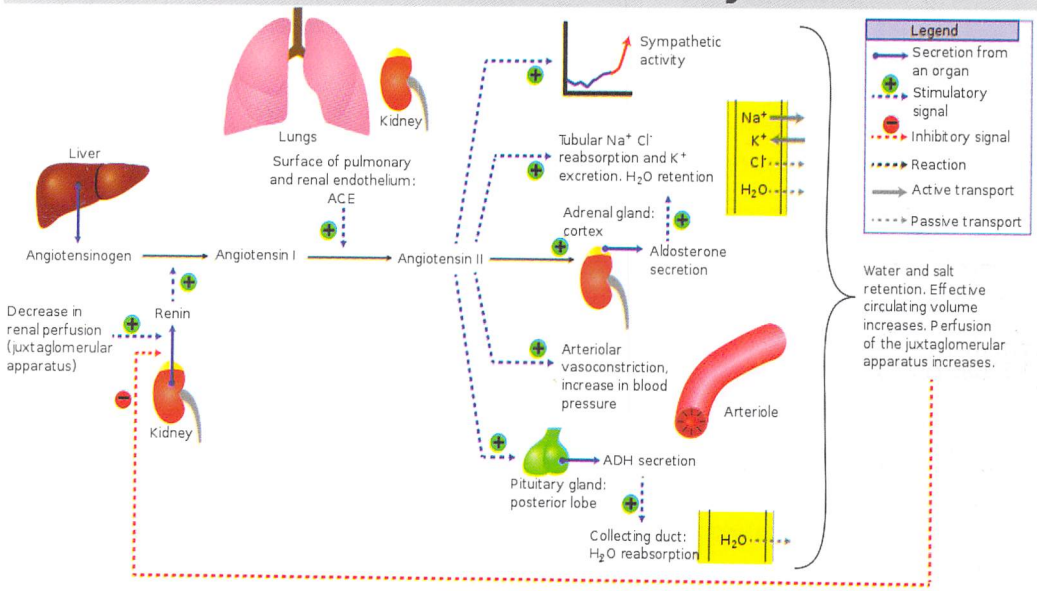
- ***Doses***;
  - **Labetalol**: (orally) ***initial***: 100 mg twice daily. ***Maintenance***: 200 to 400 mg twice daily.
    (IV) 20-80 mg to treat **hypertensive crisis**.
  - **Carvedilol**: (orally) ***initial***: 6.25 mg twice daily with food. ***Maintenance***: 6.25-25 mg twice

2) Angiotensin-Converting Enzyme Inhibitors (ACEIs)

The **hypotensive activity** of **ACE inhibitors**, ***due to***;
  - ***Blocks*** the **conversion** of **angiotensin I** to **angiotensin II**.
  - ***Inhibits*** the **degradation** of **bradykinin** (vasodilator peptide, **cause** VD via NO release).

- **Cardiac output** and **heart rate** are ***not significantly*** changed.

Renin-angiotensin-aldosterone system



Captopril (Capoten®)#	**Lisinopril** (Zestril®)#	**Enalapril** (Renitec®)#
Fosinopril (Monopril®)#	**Perindopril** (Coversyl®)#	**Ramipril** (Tritace®)#
Benazepril (Cibacen®)	**Cilazapril** (Zapritens®)	**Imidapril** (Tanatril®)#
Zofenopril (Zofecard®)	**Quinapril** (Accupril®)	**Trandolapril** (Mavik®)

ACE inhibitors are easily identifiable by their common suffix, '**-pril**'.
All* ACE inhibitors** are ***orally bioavailable as a **drug** or **prodrug**.
All* ACE inhibitors** are given as **prodrug** to ***improve* oral bioavailability**, ***except* Captopril** and **Lisinopril**, ***so *these agents* may be ***preferred*** in **patients *with* severe hepatic impairment**.
Captopril is the ***first* ACE inhibitor**, and has a **shorter duration** of ***action***, and the ***only* sulfur-containing ACE inhibitor**; **sulfonamide allergy**.
Enalapril is an oral ***prodrug*** that is *converted to* **Enalaprilat**.
Enalaprilat is the ***only*** drug in this class **available *intravenously***.
Fosinopril is the ***only* ACE inhibitor** that is ***not eliminated*** primarily by the **kidneys** and does ***not require* dose adjustment** in patients with **renal impairment**.
ACE inhibitors *used* alone or in **combination**.
ACE inhibitors are ***first-line drugs*** for **hypertensive patients** *with* **diabetes**, **chronic kidney disease**, and patients at increased risk of **coronary artery disease**.

ACEIs precautions; # # # # # # # # **PATIENT COUNSELLING** # # # # # # #

1) **Hypotension *may occur* after initial dose**.
2) **Avoid K^+ supplements, diet rich in K^+** and ***other drugs that* increases K^+ level** in the blood e.g. **ARBs**, **Aliskiren** and **K^+ sparing diuretics**; may cause ***life-threatening* hyperkalemia**.
3) **Dry persistent cough** and **angioedema** (>20%of patients); due to ***increase*** levels of **bradykinin** and **substance P**, this effect **resolves *within* a few days** of **discontinuation**. Can be treated by (***two studies suggested***);
   - **Iron supplements** (e.g. **Ferrous sulfate**) an ***inhibitor*** of **NO synthase**.
   - **NSAIDs**; (e.g. **Aspirin** 500 mg/day).
4) **Contraindicated *with* pregnancy**; ***increase* risk** of **fetal malformation** (**fetal lung hypoplasia** and **skeletal deformities**).
5) **Other *drug interactions***;
   - ***Increase* serum level** of **Lithium**.
   - **NSAIDs**; ***reduce* hypotensive effects** of **ACE inhibitors**.

3) Angiotensin II Receptor Blockers (ARBs)

Losartan (Cozaar®)#	**Valsartan** (Diovan®)# (Tareg®)#	**Candesartan** (Atacand®)#
Irbesartan (Aprovel®)#	**Eprosartan** (Teveten®)	**Telmisartan** (Micardis®)#
Olmesartan (Erastapex®)	**Fimasartan** (Kanarb®)	**Azilsartan** (Edarbi®)

ARBs *used* alone or in **combination**. **ARBs** have a ***similar benefits*** to those of **ACE inhibitors** in patients with **hypertension**, **heart failure** and **chronic kidney disease**.
ARBs *more selective blockers* of **angiotensin effect** than **ACE inhibitors**.
ARBs have a ***similar precautions*** to **ACE inhibitors**, but ***less*** in **cough** and **angioedema**.

4) Direct Renin Inhibitors

Aliskiren (Tekturna®)#

- **Aliskiren** is the ***first*** and ***only*** drug **available** in a **class** (FDA approval in 2007).
- It is ***used*** in **treatment of hypertension** (***alone*** or in ***combination***).
- It has **long duration of action**, used ***once daily***.

Aliskiren have a ***similar precautions*** to **ACE inhibitors**, but ***less*** < < < in **cough** and **angioedema**.

5) α-Adrenoceptor Blocking Agents

Prazosin (Minipress®)#	**Doxazosin** (Cardura®)#	**Terazosin** (Hytrin®)#

These drugs are ***selective competitive*** α_1 **receptors blockers** and ***used*** **primarily** ***in men*** *with* **concurrent hypertension and benign prostatic hyperplasia (BPH)**.

- ***Doses***;
  - **Prazosin**: (orally) ***initial***: 1 mg 2-3 times daily. ***Maintenance***: 6-15 mg/d in divided doses.
  - **Doxazosin**: (orally) ***initial***: 1 mg once daily. ***Maintenance***: 1-16 mg once daily.
  - **Terazosin**: (orally) ***initial***: 1 mg once daily at bedtime. ***Maintenance***: 1 to 5 mg once daily.

Most common side effects is **first-dose orthostatic hypotension** (***initial syncope attack or first-dose phenomenon***) this include **headache**, **dizziness** and **palpitations** ⇨ *to overcome*; the ***first dose*** must be;

1) **minimized**
2) ***Giving at*** **bed time**.

Phenoxybenzamine (Dibenzyline®)	**Phentolamine** (Rogitine®)
Tolazoline (Priscoline®)	

- **Phenoxybenzamine**, **Phentolamine**, **Tolazoline** are ***non-selective*** **α-adrenoceptor blockers**.
- The drugs are **useful in diagnosis** and **treatment** of ***pheochromocytoma***.

6) Calcium Channel Blockers (CCBs)

There are three classes of CCBs;

1) **Dihydropyridines**; ***mostly***; *selective for* **vascular smooth muscle**.
2) **Phenylalkylamines**; ***mostly***; *selective for* **cardiac muscle**.
3) **Benzothiazepines**; ***intermediate between*** **phenylalkylamines & dihydropyridines**.

CCBs are ***useful*** in the **treatment** of **hypertensive patients** who also have **asthma**, **diabetes**, and/or **peripheral vascular disease**.

All CCBs are ***useful*** in the **treatment** of **angina**. In addition, **non-dihydropyridines CCBs** are ***used*** in the **treatment** of **atrial fibrillation**.

Side effects;

- # **Hypotension**; ***Dizziness***, ***headache***, and ***feeling of fatigue*** *with*; **Dihydropyridines**.
- # **Peripheral edema** *with*; **Dihydropyridines**.
- # **First-degree atrioventricular block** and **constipation** *with*; **Verapamil**.
- # **Verapamil** & **Diltiazem** ***should be avoided*** in **patients with heart failure** or **with atrioventricular block**.
- # **Nifedipine** & **other dihydropyridines** may cause **gingival hyperplasia**.

Pregnancy; ***Generally***; **CCBs are commonly used during pregnancy and lactation** to **treat hypertension**, **arrhythmia**, and **preeclampsia**. They have also been ***used*** as **tocolytic agents** to **prevent premature labour** and its complications.

Dihydropyridines

Nifedipine (Adalat®)#	**Amlodipine** (Norvasc®)#	**Felodipine** (Plendil®)#
Isradipine (DynaCirc®)	**Lacidipine** (Lacipil®)	**Nicardipine** (Cardene®)
Lercanidipine (Care dipine®)	**Nitrendipine** (Cardif®)	**Nimodipine** (Nimotop®)

This* CCB class** is ***easily identified by the suffix "**-dipine**".

All dihydropyridines have a ***much greater affinity*** for **vascular calcium channels *than*** for **calcium channels in the heart; Show *little* interaction** with other cardiovascular drugs, such as **Digoxin**.

- **Most of these agents** have ***short half-lives*** (3 to 8 hours) following an oral dose. **Sustained-release** (**SR**) preparations are available and permit ***once-daily dosing***. **Amlodipine** has a **very long half-life** and does not require a sustained-release formulation.

- ***Indication and dosage***;

Drug	Indication (most common)	Dosage
Nifedipine	Angina, Hypertension, Raynaud's phenomenon	IV; 3-10 mcg/kg. Orally (*not SR*) 20-40 mg 3 times/d.
Amlodipine	Angina, Hypertension	5-10 mg orally once daily
Felodipine	Hypertension	5-10 mg orally once daily
Isradipine	Hypertension	2.5-10 orally twice daily
Lacidipine	Hypertension	2-6 mg orally once daily
Nitrendipine	Hypertension	20 mg orally once or twice daily
Lercanidipine	Angina, Hypertension	20-30 mg once daily at least 15 min before meals
Nicardipine	Angina, Hypertension, Cerebral vasospasm	20-40 mg orally 3 times daily
Nimodipine	Cerebral vasospasm, Subarachnoid Hemorrhage	60 mg orally every 4 hours

Nifedipine may be ***used for* migraine prophylaxis** or **premature labor**.

- **Felodipine** *interact with* **grapefruit juice** (block the CYP3A4 enzymes).

- **Nimodipine** and **Nicardipine** can ***pass* BBB** and is ***used to*** prevent **cerebral vasospasm**.

Clevidipine (**Cleviprex®**) is a ***newer agent*** that is ***formulated*** for **IV use only**.

Phenylalkylamines

Verapamil (Isoptin®)#

Verapamil has significant effects on ***both* cardiac** and **vascular smooth muscle**.

- It is the ***least effective*** of any **CCBs** on **vascular smooth muscle**.

It is ***used*** to **treat hypertension**, **angina**, **supraventricular tachyarrhythmias**, **migraine prophylaxis** and **cluster headaches prophylaxis**.

- ***Adult dose***; Orally (**not SR**) 80-160 mg orally 3 times daily.
  IV 75-150mcg/kg as bolus over at > 2 min.

Benzothiazepines

Diltiazem (Altiazem®)#

- **Diltiazem** affects ***both* cardiac** and **vascular smooth muscle**.

It is ***used*** in the **treatment** of **hypertension**, **angina**, and **supraventricular tachyarrhythmias**.

***Topical* Diltiazem** as a **2%** cream or ointment effective in **treatment chronic anal fissure**, it ***cause* muscle relaxation** and ***improve* blood flow** to ***facilitate* healing**.

- ***Adult dose***; Orally (**not SR**) 30-80 mg orally 4 times daily.
  IV 75-150mcg/kg as bolus over at > 2 min.

7) Centrally Acting Sympathetic Inhibitors

Clonidine (Catapres®)#

Clonidine is an **α_2 agonist** (*centrally* and *peripherally*) is ***used*** for **hypertension**.
- ***Adult dose***; - **Oral** (**Catapres®**) ⇨ ***Must be given*** twice a day.
  - ***Initial***; 0.1 mg tablet twice daily (morning and bedtime).
  - ***Maintenance***; 0.2-0.6 mg per day given in divided doses.
- **Transdermal** (**Catapres-TTS®**) ⇨ given once every 7 days.
- ***Side effects*** (*dose-related*); **Dry mouth, drowsiness, dizziness, constipation** and **sedation**.
Clonidine ***precautions***; # # # # # # # # **PATIENT COUNSELLING** # # # # # # #
- ***Clonidine therapy should be gradually tapered off***; **Clonidine** ***suppresses sympathetic outflow*** resulting in ***lower*** **blood pressure**, but ***sudden*** **discontinuation** can cause ***rebound*** **hypertension** (***life-threating*** **hypertensive crisis**) due to a ***rebound*** in **sympathetic outflow**. (***Treated by*** **α_1** and **β** blockers).

α-Methyldopa (Aldomet®)#

Methyldopa is an **α_2 agonist** that has *both* ***central*** and ***peripheral*** **effects**.
Used for **management of hypertension in pregnancy** (**FDA pregnancy *category* B**).
- ***Used with caution*** in **lactating women** (appears in breast milk).
- ***Adult dose***;
  - ***Initial***; 250 mg orally 2-3 times a day in the first 48 hours.
  - ***Maintenance***; 500 mg to 2 g orally divided in 2 to 4 doses, up to a maximum of 3 g/day.
  - ***Hypertensive emergency***; 250 to 500 mg IV over 30 to 60 minutes every 6 hours up to a maximum of 1 g every 6 hours or 4 g/day.

Selective Imidazoline Receptors Agonists

Rilmenidine (Hyperium®)	**Moxonidine** (Cynt®)

- ***Used*** in **mild to moderate essential hypertension**.

8) Peripherally Acting Sympathetic Inhibitors

Guanethidine (Ismelin®)

- It acts by ***blocking the release*** of stored **norepinephrine** (NE).
- ***Used*** in the treatment of ***moderate*** and ***severe*** **hypertension** and **renal hypertension**.
- ***Side effects***: **Bradycardia, orthostatic hypotension, failure of ejaculation & nasal congestion**

Reserpine (Hypoten®)#

- **Reserpine** is a **plant alkaloid** from dried root of ***Rauwolfia serpentina***.
- It acts by irreversibly blocks of monoamine neurotransmitters (norepinephrine, dopamine, and serotonin) from storage vesicles in the adrenergic nerve terminals in all body tissues.
- It has a ***slow onset***, a ***long duration*** of action.
- It is ***used*** in the treatment of **mild hypertension**.
- ***Most common side effects***: diarrhea, hyperacidity, bradycardia and nasal congestion.

9) Ganglionic Blockers (GBs)

Trimethaphan (Arfonad®)	**Mecamylamine** (Inversine®)
- Mono sulfonium (S^+).	- Secondary amine.
- Don't pass BBB.	- Pass BBB.
- Ultra short duration of action (10 to 15 min.).	- Longer duration of action.
- Not given orally (IV).	- Given orally.

10) Vasodilators

Hydralazine (Apresoline®)

Hydralazine is a ***direct vasodilator***, it **dilates arterioles *but* not veins**.
Uses; - **Severe essential hypertension**.
- ***Commonly* used in combination *with* nitrates** for the **treatment of CHF in self-identified African American populations**.
- **Oral hydralazine** is effective as **monotherapy *or*** as **add-on therapy** to **methyldopa** in the long term **management of chronic hypertension in pregnancy**.

- ***Adult dose***; - ***Oral dose***: 10 mg orally 4 times a day for the first 2 to 4 days. ***Increase*** to 25 mg orally 4 times a day for the balance of the first week. ***For the second and subsequent weeks***, increase dosage to 50 mg orally 4 times a day.
- ***Hypertensive emergency***; Usual dose: 20 to 40 mg IV or IM, repeated as necessary (patients with marked renal damage may require a lower dose).

Common side effects; **Headache, nausea, anorexia, palpitation, sweating** and **flushing**. Up to 20% of patients (how slowly acetylate the drug) who receive 400 mg/day or more mainly develop a # systemic lupus erythematosus syndrome #.

Minoxidil (Loniten®)

- **Minoxidil** is a ***very efficacious* orally active vasodilator**.
- Like **hydralazine, minoxidil dilates arterioles *but* not veins**.
- ***Because*** of its **greater potential antihypertensive effect, minoxidil *should replace* hydralazine *when* maximal dose of the hydralazine is not effective**.

Uses; - **Oral**; **Treatment of severe hypertension**.
- ***Adult dose***; 5 mg as a single daily dose, may be increased to 10, 20 and then to 40 mg. The effective dosage range is usually 10 to 40 mg per day. The maximum recommended dosage is 100 mg/day.

#**Topical** (Rogaine®); **Androgenic alopecia** in **males** and **females** and **stabilisation of hair loss** in patients with androgenic alopecia.

- ***Most common side effects;*** **Tachycardia, angina** and **edema**.
- **Headache, sweating** and **hypertrichosis**.

Sodium Nitroprusside (Nipride®)

- **Sodium Nitroprusside**, is a ***powerful* short acting parenterally vasodilator** that is ***used*** in treating **hypertensive emergencies** as well as **sever heart failure**.
- It is **dilates *both* arterial** and **venous vessels**.
- ***Pharmacokinetics***; - ***Duration of action***; 1 - 10 minutes after infusion is stopped.
- ***Dose***; 0.5 mcg/kg/min, maximum dose; 10 mcg/kg/min.
- ***Toxicity***; The most serious toxicity is related to accumulation of cyanide and may cause death. Administration of **sodium thiosulfate** (sulfur donor) facilitates cyanide metabolism. **Hydroxocobalamin (vit. B_{12})** combined with cyanide to form the non-toxic cyanocobalamin.

Diazoxide (Proglycem®)

- **Diazoxide** long acting **arteriolar dilator** that is ***used*** to **treat hypertensive emergencies**.
- It is a ***potassium channel activator***, which causes vascular smooth muscle relaxation.
- It is also **inhibits the secretion of insulin** from the pancreas, thus it is ***used*** to **counter hypoglycemia** in disease states such as insulinoma (a tumor producing insulin) or congenital hyperinsulinism.
- ***FDA warning*** (7/2015) pulmonary hypertension has been reported in infants and newborns treated with diazoxide.

Fenoldopam (Corlopam®)

- **Fenoldopam** is a ***peripheral* dopamine D_1 receptors *agonist***.
- ***Routes of administration***: for **continuous IV infusion** only ⇨ due to extensive first-pass metabolism and short half-life elimination (10 minutes).
- ***Period of administration***: up to 48 hours in adults - up to 4 hours in pediatric.
- ***Mechanism of action***: **rapid-acting vasodilator** ⇨ agonist of peripheral dopamine D_1 receptors ⇨ VD of renal blood vessels ⇨ diuresis.
- ***Uses***: **severe hypertension** in **hospitalized patients**.
- ***Dose***: initial; 0.1 mcg/kg/min, dose titrated every 15 or 20 min. to a maximum 1.6 mcg/kg/min.
- ***Adverse effects***: **Headache, flushing, dizziness, nausea** and **tachycardia**.

11) Natural Antihypertensive Agents

Hibiscus Tea (*Hibiscus sabdariffa*)

- Hibiscus flowers contain **anthocyanins**, which are believed to be the active antihypertensive compounds, acting as **ACE inhibitors**.
- There is **no difference** between drinking hibiscus **cold** ***or*** **hot**.

Co-Enzyme Q_{10}

- CoQ-10 is a natural antioxidant (is a vitamin-like substance) synthesized by the body, found in many foods & available as a supplement, found in small amounts in meats & seafood.
- CoQ10 may play a role in treating heart and **blood vessel** conditions such as **CHF**, **angina** and **hypertension**.
- CoQ10 may play a role in reducing the number and severity of **migraine headaches**, and improving ***sperm* motility** in men.

Statins have ***side effects***, including **muscle** and **joint aches**; taking a **CoQ10** *might* ***reduce*** the **risk** of these **side effects**.

➢ Special Populations:-

- Diuretics
- β-blockers
- ACEIs
- ARBs
- Renin Inhibitors

- α-blockers
- CCBs
- Centrally-acting inhibitors
- Peripherally-acting inhibitors
- Vasodilators

Population or Disease State	Preferred Agents	Avoid Agents
- African Americans and Elderly	Thiazide, CCB	
- Pregnancy	α-Methyldopa, CCB, Labetalol	ACEI, ARB, Aliskiren and >
- Coronary Diseases (Angina & MI)	β-blocker, CCB, ACEI, ARB	
- Asthma and COPD	CCB	β-blockers, ACEI, ARB
- Benign Prostatic Hyperplasia	α-blocker	
- Depression	CCB, ACEI, ARB	Centrally acting inhibitors, β-blockers, Reserpine
- Diabetes Mellitus	CCB, ACEI, ARB	β-blockers
- Gout	CCB, ACEI, ARB	Diuretics
- Heart Failure	ACEI, ARB, β-blocker	
- Hyperlipidemia	CCB, ACEI, ARB	β-blockers, Diuretics
- Migraine	β-blocker, CCB	
- Osteoporosis	Thiazide	Loop diuretics
- Peripheral Vascular Diseases	α-blockers, Dihydropyridines CCB	β-blockers
- Renal Diseases	Loop diuretics	Thiazide diuretics

Antihypotensive Drugs

Lifestyle Modification;

1) **Drink enough amount of water**; to increase blood volume.
2) **Add more salt *in* diet**; to increase blood volume.
3) **Eat healthy diet**; contains all nutrients for good health.
4) **Eat *small*, *low*-carbohydrate meals**; prevent blood pressure from dropping sharply after meals.
5) **Morning dose of caffeine**; as coffee or tablet form can be effective.
6) ***Stand up* gradually**; to reduce the dizziness and lightheadedness.
7) ***Avoid* standing for long periods of time**; to prevent neurally mediated hypotension.
8) **Wear compression stockings**; to reduce the pooling of blood in the legs.

Systolic blood pressure less than 90 mm Hg or diastolic of less than 60 mm Hg.

Sympathomimetic Agents

Etilefrine (Effortil®)#

- **Etilefrine** is a cardiac stimulant, stimulation of both α and β adrenergic receptors.
Used for **symptomatic treatment of orthostatic hypotension (OH)**.
- ***Dosage forms***; oral solution (drops), tablets and injection.
- ***Oral solution*** (10 drops = about 5 mg) should be taken with liquid ***before*** **meals**;
  - **Under 2 years**: 2-5 drops three times a day.
  - **2-6 years**: 5-10 drops three times a day.
  - **Over 6 years**: 10-20 drops three times a day.

Midodrine (Gutron®)#

- **Midodrine** is a prodrug that is hydrolysed to **Desglymidodrine**.
- **Desglymidodrine**, is an **α_1-agonist**, ***does not*** stimulate cardiac β-adrenergic receptors.
It is ***used*** orally for **symptomatic treatment of orthostatic hypotension (OH)**.
- ***Dose***; adult, 10 mg orally three times a day. Do not give more frequently than every 3 hours, after the evening meal, or less than 4 hours before bedtime. Because Desglymidodrine is excreted renally, dosing in patients with abnormal renal function should be cautious, it is recommended that treatment of these patients be initiated using 2.5-mg doses.

Heptaminol (Corasore®)#

- **Heptaminol** is a cardiac stimulant drug, it have a positive inotropic action, with a slight peripheral vasoconstrictor properties.
Uses; **hypotension, fainting tendency** and **circulatory collapse**.
- ***Dose***; - **< 12 years**: 4-16 drops (25-100 mg) depending on age, 2-4 times daily, up to 6 times daily if necessary.
  - **> 12 years**: One tablet or 25 drops, (150 mg) 2-4 times daily, up to 6 times daily if necessary.
- ***Pregnancy***; No data available.

Sympathomimetic Agents used in Hypotensive Shock

- **Epinephrine**; ***used in* anaphylactic shock**.
- **Norepinephrine**, **Dopamine** and **Dobutamine**; ***used in* cardiogenic** and **septic shock**.

Synthetic Mineralocorticoids

Fludrocortisone (Astonin-H®)#

- **Fludrocortisone** (9α-fluorocortisol or 9α-fluorohydrocortisone) is a ***synthetic* corticosteroid** with ***moderate* glucocorticoid potency** and ***much greater* mineralocorticoid potency**.
It is ***used*** primarily to replace the missing aldosterone hormone in **adrenal insufficiency** (Addison's disease), it cause ↑ salt and water retention ⇨ ↑ blood volume ⇨ ↑ CO ⇨ ↑ BP.
- ***Used with caution*** in **diabetes mellitus**, **CHF**, **glaucoma**, **children** and **pregnancy**.
- ***Most common side effects***; ankle edema, hypokalemia, headache and rarely congestive heart failure.
- ***Dose***; 0.05 to 0.1 mg orally/24 hours.

Antianginal Drugs

1) Organic Nitrates

Nitroglycerin (NitromAck®)#	**Isosorbide Mononitrate** (Effox®)#
Isosorbide Dinitrate (Isordil®)# (Dinitra®)#	**Amyl Nitrate**

- ***Doses***;
  - *Short Acting* (**Acute Attacks**):
    - **Nitroglycerin**;
      - **IV**; 5 mcg/min continuous IV infusion via non-absorptive tubing; increase by 5 mcg/min every 3 to 5 minutes as needed up to 20 mcg/min, then by 10 or 20 mcg/min if needed. N.B; Starting doses of 25 mcg/min or higher have been used with polyvinyl chloride (PVC) tubing.
      - **Lingual Spray**; 1 to 2 sprays (0.4 to 0.8 mg) on or under tongue every 5 minutes as needed, up to 3 sprays in 15 min.
      - **Sublingual Tablet**; 0.3 to 0.6 mg sublingually or in the buccal pouch every 5 min. as needed, up to 3 doses in 15 min.
    - **Isosorbide Dinitrate**;
      - **Sublingual Tablet**; 2.5-5 mg every 2 to 3 hours.
    - **Amyl Nitrite**;
      - **Inhalation**; 0.3 milliliter (1 ampule) taken by inhaling the vapour of amyl nitrite through the nose. Dose may be repeated within 1 to 5 minutes if pain is not relieved.
  - *Long Acting* (**Angina Prophylaxis**):
    - **Nitroglycerin**;
      - **Extend Release Capsule**; 2.5 to 6 mg orally 3 to 4 times a day.
      - **Topical Ointment**; 1/2 inch or 1.27 cm (7.5 mg) topically on rising in the morning and 1/2 inch (7.5 mg) 6 hours later.
      - **Transdermal Patch**; 0.2 to 0.4 mg/hr., patch applied topically once a day for 12 to 14 hr per day (patch-off 10-12 hr).
    - **Isosorbide Dinitrate**;
      - **Immediate Release**; initial: 5-20 mg orally 8-12hr, maintenance: 10-40 mg orally 8-12hr.
      - **Extended Release**; initial: 40 mg orally, maintenance: 40-80 once or twice daily.
      - **Sublingual Tablet** (***Prophylaxis***): 2.5-5 mg 15 minutes before performing activities likely to cause angina.
    - **Isosorbide Mononitrate**;
      - **Immediate Release**; 20 mg orally twice a day.
      - **Extended Release**; 30 to 60 mg orally once a day in the morning.
- ***Side effects***;

 # # Vasodilation Related Side Effects # #

- *The major acute adverse effects of organic nitrates are*: **Orthostatic hypotension** (dizziness or syncope), **throbbing headache** (cerebral vasodilation), **reflux tachycardia** & **facial flushing**.

 # # Nitrate Tolerance # #

☞ **Avoid Nitrate Tolerance**;

1) **Nitrate holiday** ("**nitrate free period**" or **NFP**) of at least 10 hours and preferably up to 14 hours is recommended to avoid tolerance;
   - *For example;*
     - Regular-release isosorbide dinitrate, which is administered 3-4 times daily, may be scheduled at 7:00 AM, Noon, and 5:00 PM.
     - Isosorbide-5-mononitrate and sustained release preparations of nitroglycerin or isosorbide dinitrate may be given twice daily at 8:00 AM and 3:00 PM, allowing a 10-12 hour nitrate holiday.
     - Removal of nitroglycerin ointment paper and residual ointment at bedtime.
     - A nitroglycerin transdermal patch placed at 8:00 AM may be removed at bedtime.
2) **Sulfhydryl group donors** like **N-acetylcysteine** (**NAC**) and **L-methionine** have been shown to potentially reduce nitrate tolerance, but they may potentiate the effects of nitrates.
3) Oral **vitamin C**, **vitamin E** (antioxidants) and **folic acid** may be effective in ameliorating nitrate tolerance.
4) **Carvedilol** (antioxidant properties) and **Nebivolol** (antioxidant properties and NO-mediated vasodilatory effects) may reduce nitrate tolerance associated with continuous nitrate therapy.

- ***Recent study***; ACEIs and ARBs may be effective in nitrate tolerance.

 # # # # Drug Interaction; **Sildenafil**, **Tadalafil**, **Vardenafil** and **Avanafil**; ***severe*** **hypotension**.

2) β-Blockers

- *See previous topic*; Antihypertensive drugs.

3) Calcium Channel Blockers (CCBs)

- *See previous topic*; Antihypertensive drugs.

4) Newer Antianginal Drugs

Ranolazine (Ranexa®)#

It is a ***newer antianginal drug*** (approved in 2006), classified as **Na^+ channel blocker**.
- ***Uses***; **treatment of chronic angina** and may be used ***alone*** or in ***combination***.
- ***Dose***; 500 mg twice daily. ***May*** increase to 1 g daily, based on symptoms (max, 2g/day).
- ***Drug interactions***; **Diltiazem**, **Verapamil**, **Erythromycin** and **grapefruit juice** and **Tricyclic antidepressants** (dose; not exceed 500 mg).
- ***Most common side effects***; **dizziness**, **headache**, **constipation** and **nausea**.
- It ***can*** **prolong QT interval** and ***should be avoided*** with other drugs that cause QT prolongation.
- ***Pregnancy***; **category C.**

Trimetazidine (Vastarel® MR)#

Trimetazidine (TMZ) is a **first cytoprotective anti-ischemic agent**.
- Trimetazidine has ***no*** **negative inotropic** or **vasodilator properties**.
- ***Uses***; ***add-on therapy*** with **stable angina pectoris**.
- ***Dose***; 20 mg 3 times a day during meals or 35 mg twice daily during meals.
- ***Contraindication***; **Parkinson disease** & ***severe*** **renal impairment** (CrCl < 30ml/min).
- ***Most common side effects***; **dizziness**, **headache**, **abdominal pain**, **diarrhea**, **dyspepsia**, **nausea**, **vomiting** and **hypersensitivity reactions**.

Nicorandil (Randil®)#

- Nicorandil is a ***new organic nitrate with vasodilator properties***.
- Nicorandil has the ***dual properties*** of a **nitrate** and **potassium channel activators**.
- ***Dose***; 10 mg twice, may increase this dose if necessary, max. dose is 30 mg twice daily.
- ***Most common side effects***; headaches, dizziness, flushing and reflex tachycardia.

Ivabradine (Procoralan®)#

- It was approved by the European Medicines Agency (EMA) in 2005 & by FDA in 2015
- It is ***indicated for*** the **symptomatic treatment of chronic stable angina pectoris** in patients with normal sinus rhythm who cannot take β-blockers or in combination with β-blockers in patients inadequately controlled with an optimal beta-blocker dose.
- It is ***also indicated*** in **combination *with* beta blockers** in **heart failure** patients with left ventricular ejection fraction lowers than 35% inadequately controlled by β-blockers alone and whose heart rate exceeds 70 beats per minute.
- ***Dose***; starting dose 5 mg twice. The maintenance dose usually 7.5 mg twice daily.
- ***If there is no improvement within 3 months***, **Ivabradine** should be discontinued.
- ***Most common side effects***; luminous phenomena or phosphenes (seeing light without light actually entering the eye), first-degree AV block, ventricular extrasystoles, dizziness and/or blurred vision.
- ***Drug interactions***; **Liver CYP3A4 inhibitors**.

Drugs for Heart Failure (HF)

- ***Treatment options of*** acute decompensated heart failure (**ADHF**) ***is different from*** treatment options of chronic heart failure (**CHF**).

		ADHF	CHF
1) Angiotensin-Converting Enzyme (ACE) Inhibitors			✓
2) Angiotensin II Receptor Blockers (ARBs)			✓
3) Angiotensin-Receptor Neprilysin Inhibitors (ARNIs)			✓
4) β-Adrenergic Blocking Agents (β-Blockers)			✓
5) Diuretics	A) Loop Diuretics	✓	✓
	B) Thiazide Diuretics	✓	✓
6) Aldosterone Antagonists			✓
7) Vasodilators	A) Hydralazine + Isosorbide Dinitrate		✓
	B) Na^+ Nitroprusside or IV Nitroglycerin	✓	
	C) Nesiritide	✓	
8) Inotropic Agents	A) Cardiac Glycosides		✓
	B) β-Adrenergic Agonists	✓	
	C) Phosphodiesterase III Inhibitors	✓	

- ✓; Drugs which are used.
- ADHF; Acute Decompensated Heart Failure.
- CHF; Chronic Heart Failure.

1) ACE Inhibitors

ACEIs ***should be prescribed*** to **all patients *with* HF*r*EF** (HF with reduced ejection fraction), ***unless*** there is a **contraindication**.

- ***Monitoring***; renal function and serum K^+ should be assessed within 1-2 weeks of initiation of therapy, recheck at 1, 3 and 6 months, if the function is normal perform it every 6 months.
- *See previous topic*; **Antihypertensive drugs**.

2) ARBs

ARBs are *recommended* in **patients with HF*r*EF with current or prior symptoms who are unable to take an ACE inhibitor**.

- *See previous topic*; **Antihypertensive drugs**.

3) Angiotensin-Receptor Neprilysin Inhibitors (ARNIs)

Sacubitril/Valsartan (Entresto®)#

#**ARNIs** are a ***new drug combination*** of a **neprilysin inhibitor** and an **ARB**.
- First approved by FDA in July 7th, 2015.
- **Entresto®** an oral fixed-dose combination of the ***neprilysin inhibitor*** **Sacubitril** and the ***angiotensin receptor blocker*** (**ARB**) **Valsartan**.

Used in ***conjunction with*** other **heart failure therapies**, ***in place of*** an **ACE inhibitor** or ***other*** **ARBs**.
- **Sacubitril** is a ***pro-drug*** that is activated to LBQ657, which inhibits neprilysin enzyme.
- ***The recommended starting dose*** of **Entresto®** is 49/51 mg (Sacubitril/Valsartan) twice-daily. Double the dose of **Entresto®** after 2 to 4 weeks to the target maintenance dose of 97/103 mg (Sacubitril/Valsartan) twice-daily.

4) β-Blockers

Three **β-blockers have been shown to be effective in reducing the risk of death in patients with chronic HF*r*EF**: **Bisoprolol**, **Carvedilol**, and **Metoprolol Succinate**.
- **β-blockers** ***should be*** **prescribed** to **all patients** ***with*** **HF*r*EF** ***unless*** they have a contraindication to their use or are intolerant of these drugs.
- *See previous topic*; **Antihypertensive drugs**.

5) Diuretic Agents

Diuretics are ***recommended*** in **patients** ***with*** **HF*r*EF** ***who have evidence of*** **fluid retention**.
- **Loop diuretics** are ***preferred*** diuretic agents for use in most patients with HF.
- ***Should be*** prescribed to **all patients** ***with*** **fluid retention**.
- ***Should be combined with*** an **ACE inhibitor**, **β-blocker** and **aldosterone antagonist**.
- *See previous topic*; **Antihypertensive drugs**.

6) Aldosterone Antagonists

- **Aldosterone antagonists** are ***recommended in patients with***;
  - **Patients with NYHA class II-IV HF and who have LVEF of 35% or less**.
  - **Patients with HF*r*EF after myocardial infarction**.
- ***Should be added*** to **ACE inhibitor**, **β-blocker**.
- ***Monitoring***: **K^+ levels** and **renal function** ***should be*** rechecked within 2 to 3 days and again at 7 days after initiation of therapy.
- *See previous topic*; **Antihypertensive drugs**.

7) Vasodilators

A) Hydralazine + Isosorbide Dinitrate (*only for CHF*)

The combination of **Hydralazine** and **Isosorbide Dinitrate** (**BiDil®**) are ***recommended in addition to*** **ACE inhibitors + β-blockers to reduce morbidity and mortality for patients self-described as African Americans with HF*r*EF**.

The combination of **Hydralazine** and **Isosorbide Dinitrate** (**BiDil®**); ***may be useful*** in **patients with current or prior symptoms of HF*r*EF who are unable to tolerate an ACEI or an ARB**.
- ***Dosing and administration:***

Initial Dose	Target Dose
37.5 mg hydralazine + 20 mg ISDN 3 times daily	75 mg hydralazine + 40 mg ISDN 3 times daily

B) Na^+ Nitroprusside or IV Nitroglycerin (*only for* ADHF)

- **Sodium Nitroprusside** (Nipride®); ***useful for*** **patients with ADHF and advanced HF.** ***Typical dose***; 0.5-1 mcg/kg/minute IV.
- **IV Nitroglycerin**; is a rapid and short acting organic nitrate, it produces venous vasodilation ***reductions*** in **preload, arterial BP** and ***relief*** **pulmonary congestion** make it particularly ***useful for*** **patients with ADHF.** ***Typical dose***; 25-75 mcg/minute IV, titrated to response.

C) Nesiritide (*only for* ADHF)

- **Nesiritide** (Natrecor®); ***Used in*** **patients with ADHF who have dyspnea at rest or with minimal physical activity.**
- ***Typical dose***; 0.01 mcg/kg/minute IV, May omit bolus if low systolic blood pressure.

8) Inotropic Agents

A) Cardiac Glycosides

Digoxin (Lanoxin®)# | **Digitoxin** (Unidigin®) | **Ouabain** (Uabanin®)

Digoxin therapy is ***indicated*** in **patients with severe HF*r*EF after initiation of ACE inhibitor, β-blocker** and **diuretic therapy.**
- ***Better results*** are obtained in **patients with atrial fibrillation or flutter.**
- ***Dose***;
  - **Digoxin**; **0.125 to 0.25 mg daily** or ***every*** **other day**
  - **Monitoring Serum Digoxin Concentration** (**SDC**); range of 0.5 to 0.9 ng/mL.

Side effects;
- **Major side effect** is **cardiac arrhythmia.**
- ***Early manifestation of toxicity***; **Anorexia, nausea** and **vomiting** and **bradycardia.**
- ***Late manifestation of toxicity***;
  - ***Eye***; **Visual disturbance** (**Chromatopsia** or **Xanthopsia**).
  - ***CVS***; **Arrhythmias.**
  - ***GIT***; **Anorexia, nausea, vomiting** and **diarrhea.**
  - ***CNS***; **Hallucination, convulsions, confusion** and **delusions.**
  - ***Endocrine***; **Gynecomastia** (rare).

Factors that increase digitalis toxicity; **### PATIENT COUNSELLING ###**

- **Drugs increase toxicity** e.g. thiazide and loop diuretic (hypokalemia).
- **Organ dysfunction** e.g. Kidneys (Digoxin) and liver (Digitoxin).
- **Dosing** ***errors***.
- **Old age** (>70 years of age).
- **Serum electrolytes disturbances**: hypokalemia, hypomagnesaemia or hypercalcemia.

Digoxin Immune Fab (Ovine) (Digibind®)#

Digoxin Immune Fab (**Ovine**), is a sterile lyophilized powder of antigen binding fragments (Fab) ***derived from*** specific **antidigoxin antibodies** raised in sheep (Ovine).
Digoxin Immune Fab (**Ovine**), is ***indicated for*** **treatment of potentially life-threatening digoxin intoxication.**
- ***Dose***;

A) Skin Testing.

B) Dose Calculations;

TABLE : Adult Dose Estimate of DIGIBIND (in # of vials) from Steady-State Serum Digoxin Concentration

	Serum Digoxin Concentration (ng/mL)						
Patient Weight (kg)	**1**	**2**	**4**	**8**	**12**	**16**	**20**
40	0.5 v	1 v	2 v	3 v	5 v	7 v	8 v
60	0.5 v	1 v	3 v	5 v	7 v	10 v	12 v
70	1 v	2 v	3 v	6 v	9 v	11 v	14 v
80	1 v	2 v	3 v	7 v	10 v	13 v	16 v
100	1 v	2 v	4 v	8 v	12 v	16 v	20 v

v = vials

B) β-Adrenergic Agonists (only for ADHF)

Dopamine (Intropin®)#	Dobutamine (Dobutrex®)#

Dopamine; is a cardiac stimulant drug (**β_1 agonist effect**) ⇨ +ve inotropic. It has renal blood vessels dilatation effect (**D_1 agonist**) ⇨ increase blood flow to the kidneys).

Dobutamine is a ***predominantly*** **β_1 receptor agonist** ⇨ improve cardiac performance by causing positive inotropic effects with slight peripheral vasodilation.

- **Dobutamine** is ***the most commonly used*** **inotropic agent**.
- **Dobutamine** ***typical dose***; 5 mcg/kg/minute IV.
- ***Both drugs*** must be given by IV infusion and are primarily ***used in*** the **short-term treatment of ADHF** in the hospital setting.

C) Phosphodiesterase III Inhibitors (only for ADHF)

Amrinone (Inocor®)#	Milrinone (Primacor®)#

Both drugs must be given by IV and are primarily ***used in*** the **short-term treatment of ADHF** in the hospital setting.

- ***Dose***; - **Amrinone**; 0.75 mg/kg IV bolus over 2-3 minutes, then 5-10 mcg/kg/min IV.
  - **Milrinone**; 50mcg/kg IV bolus, then 0.375 mcg/kg/min IV.
- ***Side effects***; Arrhythmia, Hypotension and Thrombocytopenia.

Antiarrhythmic Drugs

Class/Ion Affected	Agents	Physiologic Effect	Result on Electrophysiologic Parameters	Clinical Utility
Class I (Na^+ channel blockers)				
IA (intermediate)	Quinidine Disopyramide Procainamide	↓ Conduction velocity ↑ Refractory period	↑ QRS complex and ↑ QT interval	Atrial and ventricular arrhythmias
IB (fast)	Lidocaine Mexiletine	↓ Conduction velocity ↓ Refractory period	↓ QT interval	Ventricular arrhythmias
IC (slow)	Flecainide Propafenone	↓↓↓ Conduction velocity Ø Refractory period	↑ QRS complex	Supraventricular arrhythmias and ventricular arrhythmias
Class II (β-Blockers)	Metoprolol Esmolol Atenolol	↓ Conduction velocity ↑ Refractory period	↓ HR and ↑ PR interval	Atrial and ventricular arrhythmias
Class III (K^+ channel blockers)	Amiodarone Dronedarone Sotalol Dofetilide Ibutilide	Ø Conduction velocity ↑↑↑ Refractory period	↑ QT interval	Atrial and ventricular arrhythmias
Class IV (Ca^{2+} channel blockers)	Diltiazem verapamil	↓ Conduction velocity ↑ Refractory period	↓ HR and ↑ PR interval	Atrial and ventricular arrhythmias

1) Class I (Sodium Channel Blockers)

A) Class IA

Quinidine (Quinacard®) | **Procainamide** (Pronestyl®) | **Disopyramide** (Norpace®)

- **Quinidine**; **Atrial fibrillation/flutter** and **ventricular tachycardia**.
  - ***Dose***; As Sulfate: 200–400 mg orally every 6 hours.
    As Gluconate (CR): 324 mg orally every 8-12 hours.
- **Procainamide**; **Atrial fibrillation/flutter conversion**: 1 g IV for 30 min; then 2 mg/min.
  - **Ventricular tachycardia conversion**: 20 mg/min IV until 17 mg/kg or arrhythmia is controlled.
  - **Ventricular tachycardia maintenance**: 1-4 mg/min.
    (reduce dose in renal and liver dysfunction)
- **Disopyramide**; **Atrial fibrillation/flutter conversion**: Immediate-release (IR) 200 mg (if <50 kg) or 300 mg (if >50 kg) orally/6 hours.
  - **Atrial fibrillation/flutter maintenance**: IR 150 mg orally every 6 hours or as controlled release (CR) 300 mg orally every 12 hours, dose adjustment if; <50 kg, moderate renal dysfunction or hepatic dysfunction.

Side effects;

- **Quinidine**; ***common side effects***; **nausea, vomiting, diarrhea** and **Cinchonism** or **Quinism** (**blurred vision, tinnitus, headache, disorientation** and **psychosis**).
- **Procainamide**; ***common side effects***; **hypotension** (IV).
- **Disopyramide**; ***common side effects***; **anticholinergic effects** (**dry mouth, urinary retention, blurred vision** and **constipation**).
- ***Both*** **Quinidine** and **Disopyramide** should be ***used with*** **caution** with ***potent*** **inhibitors** of **CYP3A4**.

B) Class IB

Lidocaine (LidoPen®) | **Mexiletine** (Mexitil®)

Lidocaine is the ***agent of choice*** for ***termination*** of **ventricular tachycardia** and ***prevention*** of **ventricular fibrillation after acute myocardial infarction**.

- **Mexiletine** is indicated for the ***treatment*** of **ventricular tachycardia**.

Side effects;

- **Lidocaine** has a **wide therapeutic index**, ***common side effects***; CNS effects; nystagmus (early indicator of toxicity), drowsiness, slurred speech, paresthesia, agitation, confusion and convulsions.
- **Mexiletine** has a **narrow therapeutic index** and caution should be used when administering the drug with inhibitors of CYP2D6, ***common side effects***; nausea, vomiting, and dyspepsia.

C) Class IC

Flecainide (Tambocor®) | **Propafenone** (Rythmol®)

- **Flecainide**;
  - **Atrial fibrillation/flutter conversion**; 300 mg orally once.
  - **Atrial fibrillation/flutter maintenance**, **Ventricular tachycardia**, **Wolff-Parkinson-White Syndrome** and **Supraventricular tachycardia**; 50-150 mg orally/12 h.
- **Propafenone**;
  - **Atrial fibrillation/flutter conversion**: 600 mg orally once.
  - **Atrial fibrillation/flutter maintenance**, **Ventricular tachycardia**, **Wolff-Parkinson-White Syndrome**; *Immediate release*: 150-300 mg orally every 8-12 hours.
    - *Extended release*: 225-425 mg orally every 12 hours.
- ***Side effects***; **blurred vision, dizziness** and **nausea**.
- **Propafenone**; may cause **bronchospasm**
- ***Both*** **drugs** should be used *with* **caution** with ***potent*** **inhibitors** of **CYP2D6**.

2) Class II (β-blockers)

- Class II are ***useful in treating*** **tachyarrhythmias** caused by increased sympathetic activity.
- They are also ***used for*** **atrial flutter** and **fibrillation** and for **AV nodal reentrant tachycardia**. In addition, β-blockers ***prevent*** **life-threatening ventricular arrhythmias following a myocardial infarction**.
- **Esmolol** is a ***short acting*** **β-blocker** used primarily as an ***antiarrhythmic drug for*** **intraoperative and other acute arrhythmias**.
- **Sotalol** is a ***nonselective*** **β-blocker** that prolongs the action potential ⇨ **class III action**.
- *See previous topic*; **Antihypertensive drugs**.

3) Class III (Potassium-Channel Blockers)

Amiodarone (Cordarone®)#

Structure; **Amiodarone** ***contains*** **iodine** and is related structurally to **Thyroxine**.
Bioavailability; bioavailability = 35-65% (***due to*** variably absorption).
Onset of action; may occur in 2 to 3 days, but more commonly takes 1 to 3 weeks, even with loading doses.
Elimination half-life; is a complex, with a rapid component of 3-10 days (50% of the drug) and a slower component of several weeks.
After discontinuation of the drug; effect are maintained for 1-3 months.
Metabolism; **Amiodarone** is metabolized to **des-ethyl-amiodarone** (DEA) by CYP3A and CYP2C8. Dose should be reduced by up to 50% in substantial liver impairment
Elimination; biliary excretion.
Dosage Guidelines for Amiodarone;

Life-threatening arrhythmia	150-mg IV bolus over 10 minutes (if necessary, bolus may be repeated in 10 to 30 minutes); then 1 mg per minute for 6 hours; then 0.5 mg per minute for 18 hours; then reduce IV dosage or convert to oral dosing when possible.
Ventricular arrhythmia	800 to 1,600 mg per day in divided doses until a total of 10 g has been given; then 200 to 400 mg per day.
Atrial fibrillation	600 to 800 mg per day in divided doses until a total of 10 g has been given (may use higher initial dosage or IV dosing in unstable inpatients); then 200 mg per day.

Toxicity; **Pulmonary fibrosis** 3-17%, **hyperthyroidism** 3%, **hypothyroidism** 30% (**amiodarone-induced thyrotoxicosis**; **AIT**), **neurologic toxicity** 20-40%, **GI upset**, **photosensitivity**, **hepatitis**, **blue-gray skin discoloration** 15%, **heart block** 14%, **hypotension** (IV) and **phlebitis** (IV).
- ***Most common drug interaction***; **Warfarin**, **Digoxin** and **Statins**.
Finally; Keep an eye on **Amiodarone patients**.

Dronedarone (Multaq®)# (Dronadex®) (Vasodarone®)

Dronedarone is a ***non-iodinated*** **Amiodarone** **derivative**.
Pharmacokinetics; ***less*** **lipophilic**, has ***lower*** **tissue accumulation** and has a ***shorter*** serum **half-life** than amiodarone.
Side effects; **Dronedarone** has a ***better*** **adverse effect profile** than **Amiodarone** ***but*** **may still cause liver failure**.
Uses; **Dronedarone** is used to maintain sinus rhythm in **atrial fibrillation** or **flutter**, ***but*** it is **less effective** than **Amiodarone**.
- ***Dose***; 400 mg orally 2 times a day with a meal.
- ***FDA Warning***; Dronedarone is ***contraindicated*** in **patients with symptomatic heart failure with recent decompensation requiring hospitalization** or **NYHA class IV heart failure**.
- **Celivarone** is another ***non-iodinated*** **Amiodarone** **derivative** similar to **Dronedarone** that is currently undergoing clinical trials (Sanofi-Aventis) for the prevention of ventricular recurrence.

Sotalol (Betacor®)#

Sotalol is a ***non-selective*** **competitive β-adrenergic receptor blocker** that also exhibits **Class III antiarrhythmic properties**.
- The ***l*-sotalol** has **β-blocking activity**, and ***d*-sotalol** has **class III antiarrhythmic action**.
Uses; **atrial fibrillation**, **atrial flutter** and **ventricular arrhythmias**.
- ***Dose***; - ***Initial***: 80 mg orally 2 times a day, **dose *should be* adjusted** gradually every 3 days.
  - **Dose should be *adjusted*** in people with a creatinine clearance rate below 40 mL/min.
- ***Side effects***; This drug can cause the typical **adverse effects *associated*** with **β-blockers *but*** has a ***low rate*** of **adverse effects *when compared*** to **other antiarrhythmic agents**.

Dofetilide (Tikosyn®)

- **Dofetilide** is a pure potassium channel blocker, ***dose***; 125-500 mcg twice a day.
- ***Uses***; It is approved for the maintenance of normal sinus rhythm in patients with **atrial fibrillation**.
- ***Because*** of the **risk of pro-arrhythmia,** **treatment with Dofetilide** ***should be initiated*** **in hospital** ***after baseline measurement*** of **rate corrected QT interval** and **serum electrolytes**.

Ibutilide (Corvert®)

- **Ibutilide** is a **potassium channel blocker *that also have*** **action on the slow sodium channel** (**mixed class III and IA action**).
- It is ***used*** for the **acute conversion of atrial flutter** and **atrial fibrillation** (more effective in atrial flutter than atrial fibrillation) to normal sinus rhythm.
-***Because*** of the **risk of pro-arrhythmia,** **treatment with Ibutilide** ***should be initiated*** **in hospital** ***after baseline measurement*** of the **rate corrected QT interval** (QT c).

Vernakalant (Brinavess®)

- **Vernakalant** is a **multi-ion channel blocker** that was ***developed for*** the treatment of **atrial fibrillation** (final approval for this purpose is pending).
- **Vernakalant** does ***not change*** the **QT interval** on the **ECG**.
- ***Side effects***; **dysgeusia** (disturbance of taste), **sneezing**, **paresthesia**, **cough** and **hypotension**.

4) Class IV (Calcium Channel Blockers)

Verapamil (Isoptin®)# | Diltiazem (Altiazem®)#

- **Verapamil** shows ***greater action*** on the **heart *than*** on **vascular smooth muscle**, and **Diltiazem** is ***intermediate*** in its ***actions***.
- ***Uses***;
  - **Supraventricular tachycardia** is the ***major arrhythmia*** **indication** for **Verapamil**.
  - **Verapamil** can also ***reduce*** the **ventricular rate in atrial fibrillation and flutter**.
  - **Diltiazem** **appears** to be ***similar*** in **efficacy** to **Verapamil** in the management of **supraventricular arrhythmias**, including **rate control in atrial fibrillation**.

5) Miscellaneous Antiarrhythmic Agents

Digoxin (Lanoxin®)#

Digoxin is used to control **atrial fibrillation** and **flutter**.
- ***Note***: Serum digoxin concentrations of 1-2 ng/mL are desirable for atrial fibrillation or flutter, whereas lower concentrations of 0.5 to 0.8 ng/mL are targeted for systolic heart failure.

Adenosine (Adenocard®)#

IV adenosine is the ***drug of choice*** for **acute supraventricular tachycardia**.
- **Adenosine** has an ***extremely*** **short duration of action** (approximately 10 to 15 seconds) due to rapid uptake by erythrocytes and endothelial cells.
- ***Dose***; It is usually given in a **bolus** dose of **6 mg *followed***, if necessary, by a dose of **12 mg**.
- ***Toxicity***; **flushing** (20%), **chest pain** (10%) and **hypotension**.

Magnesium Sulfate

IV magnesium sulfate ***used for*** patients with **digitalis-induced arrhythmias *who were*** **hypomagnesaemia**, ***dose*** is 1 g (as sulfate) given IV over 20 min & repeated once if necessary.

Antithrombotic Drugs

Antithrombotics Classification:

1) **Anticoagulants**; limit the ability of the blood to clot.
2) **Thrombolytic *or* Fibrinolytic Drugs**; act to dissolve clots after they have formed.
3) **Antiplatelet Drugs**; limit the migration or aggregation of platelets.

Anticoagulant Drugs

Anticoagulants Classification (Mechanism):

1) **Indirect Thrombin Inhibitors (Heparins).**
2) **Direct Thrombin Inhibitors (DTIs).**
3) **Direct Factor Xa Inhibitors.**
4) **Vitamin K Antagonist (Coumarin Anticoagulants).**

Heparins

Unfractionated Heparin (UFH)

Heparin (Calciparine®) (Cal-heparin®)#

Low Molecular Weight Heparins (LMWHs)

Enoxaparin (Clexane®)# | **Dalteparin** (Fragmin®)# | **Tinzaparin** (Innohep®)#

Must be administrated; **SC** or **IV** ***only***.
Avoid* IM**; ***cause; irritation, erythema, pain, hematoma or ulceration.
UFH; ***inhibition*** of **thrombin** about 1000-fold ***and*** **factor Xa**.
LMWHs; One molecules ***bind*** to with **AT-III** ⇨ ***inactivate*** **factor Xa**.
These agents are used for;
- ***Treatment of*** **acute venous thromboembolism (DVT** or **PE)**.
- ***Prophylaxis of*** **postoperative venous thrombosis *in patients*** **undergoing surgery and those with acute MI**.
- ***Drug of choice for using in*** **pregnant women**.

- ***Doses***;
  - **UFH**;
    - ***Initial bolus injection***; 80-100 units/kg, followed by;
      Continuous infusion; 15-22 units/kg/h (*monitoring is needed*).
    - ***Prophylaxis***; 5000 units SC every 8–12 h (*monitoring is needed*).
  - **Enoxaparin** (**Clexane®**); SC 30 mg twice daily or 40 mg once daily, *alternatively*; 1 mg/kg SC every 12 hours or 1.5 mg/kg once a day.
  - **Dalteparin** (**Fragmin®**); 200 units/kg once a day for venous disease or 120 units/kg every 12 hours for acute coronary syndrome.
  - **Tinzaparin** (**Innohep®**); 175 units/kg SC once daily.

Monitoring of Heparin Effect; by **Activated Partial Thromboplastin Time (aPTT)**.
Side effects;
1) **Bleeding**; ***Monitoring*** is **required** to minimize bleeding.
   - ***Excessive bleeding*** may be **managed** by **discontinuing** the drug ***or*** by ***treating*** with **protamine sulfate**; - For every **100 units of heparin** remaining in the patient, **1 mg of protamine sulfate** is given **IV infusion** (rate ***should not exceed*** 50 mg in any 10-minute period).
2) **Hypersensitivity Reaction**; chills, fever, urticaria, and anaphylactic shock.
3) **Thrombocytopenia**; **Heparin-induced thrombocytopenia (HIT)**
4) ***Other Side Effects***; - **Osteoporosis** has been observed in patients on long-term therapy.
   - **Hair loss** and **alopecia** have been reported.

Direct Thrombin Inhibitors (DTIs)

Parenteral Direct Thrombin Inhibitors

Bivalirudin (Angiomax®) | **Lepirudin** (Refludan®) | **Desirudin** (Iprivask®)

Uses; - **Bivalirudin** also ***inhibits*** **platelet activation** and has been FDA-approved for use in **percutaneous coronary intervention (PCI)**.
- ***Dose***; initial: 0.75 mg/kg *IV bolus*, followed by *continuous infusion*: 1.75 mg/kg/hour over 4 hours, may be continued at 0.2 mg/kg/hour for up to 20 hours, patients should also receive aspirin 300-325 mg/day.

- **Lepirudin** is approved by the FDA for use in **patients with thrombosis related to heparin-induced thrombocytopenia (HIT)**.
- ***Dose***; Initial: 0.4 mg/kg *IV slowly* (over 15 to 20 seconds) followed by 0.15 mg/kg/hr IV *continuous infusion* for 2 to 10 days or longer if clinically needed.

- **Desirudin** is approved by the FDA for use for ***prophylaxis*** of **deep vein thrombosis**, ***which may lead to*** **pulmonary embolism**, ***in patients undergoing*** **elective hip replacement surgery**.
- ***Dose***; 15 mg SC every 12 hr; initiate 5-15 min before surgery (but after induction of regional block anesthesia) and continue for 9-12 days.

- ***Side effects***; ***Like the others***, **bleeding** is the major side effect of these agents.
- Up to 40% of patients who receive long-term infusions of **Lepirudin** develop an **antibody**, which may develop **life-threatening anaphylactic reactions**.

Argatroban (Argatroban®)

Uses; - ***Prophylaxis*** or ***treatment*** of **thrombosis** in **patients with heparin-induced thrombocytopenia (HIT)**.
- ***During*** **percutaneous coronary interventions (PCI)** in **patients who have HIT** or **are at risk for developing it**.

- ***Dose***; ***Before*** administering Argatroban; ***discontinue*** **heparin therapy** and ***obtain*** a **baseline aPTT**. The recommended ***initial dose*** for adult patients without hepatic impairment is **2 mcg/kg/min** as a continuous infusion, ***monitoring is needed*** (aPTT).
- ***Side effects***; As with other anticoagulants, the major side effect is **bleeding**.
- ***Contraindication***; Patients with hepatic impairment.

Oral Direct Thrombin Inhibitors

Dabigatran Etexilate (Pradaxa®)#

Pharmacokinetics; **Dabigatran Etexilate** is the ***prodrug*** of the active moiety **Dabigatran**.
Oral bioavailability is 3-7%.
Oral bioavailability ***may increase*** by up to **75%** when pellets are ***taken out*** of the **hydroxypropylmethylcellulose (HPMC) capsule**. Therefore, capsules ***should not*** be opened and pellets taken alone.
- The **half-life** of the drug is 12-17 hours.
- **Renal impairment** results in ***prolonged drug clearance*** and may **require dose adjustment** (***should be*** **avoided** in patients with **severe renal impairment**).

Uses; - ***Prevention*** **of stroke in non-valvular atrial fibrillation**.
- ***Prevention*** **of venous thromboembolism (DVT** and **PE)** ***in patients who have undergone*** **hip** ***or*** **knee replacement surgery**.

- ***Dose***; - For patients with creatinine clearance (CrCl) **>30 mL/min**; **150 mg** taken orally, ***twice daily***.
- For patients with severe renal impairment (CrCl **15-30 mL/min**); **75 mg** ***twice daily***.
- ***No*** **monitoring** is required.

- ***Side effects***; The ***primary*** **toxicity** is **bleeding**, ***GI adverse effects*** are common with this drug and may include **dyspepsia**, **abdominal pain**, **esophagitis**, and **GI bleeding**.

- ***Drug interactions***; **Ketoconazole**, **Amiodarone**, **Quinidine**, **Clopidogrel** ***increases drug effect***

Dabigatran ***antidote***; **Idarucizumab** (**Praxbind®**) is a monoclonal antibody and the ***first*** **reversal agent** for the **Dabigatran** has been approved by the FDA in October 16, 2015.

Direct Factor Xa Inhibitors

Parenteral Direct Factor Xa Inhibitors

Fondaparinux (Arixtra®)#

Fondaparinux is a ***pentasaccharide anticoagulant*** that is synthetically derived, is a chemically related to ***low molecular weight heparins*** (***LMWHs***).

- ***Pharmacokinetics***; - **SC *administration***. - ***Long*** half-life; 15 hours (once-daily).

Uses; ***Treatment*** or ***prophylaxis*** of **venous thromboembolism** (**DVT** and **PE**).

- ***Dose***; **A) *Treatments***; - Under 50 kg: 5 mg subcutaneously once a day.
  - 50 to 100 kg: 7.5 mg subcutaneously once a day.
  - Over 100 kg: 10 mg subcutaneously once a day.

  B) *Prophylaxis*; 2.5 mg SC once a day for 5 to 9 days.

- ***Side effects***; Major side effect is **bleeding** (***no antidote***).

- ***Contraindication***; Patients with **severe renal impairment** (CrCl less than 30 mL/min).

FDA warning; **Fondaparinux *should not be* used in the setting of lumbar puncture or spinal cord surgery, *Due to* risk of epidural or spinal hematomas.**

Oral Direct Factor Xa Inhibitors

Rivaroxaban (Xarelto®)# (Andorivaban®)#

Rivaroxaban is the first ***oral selective* factor Xa *inhibitor*** approved by the FDA in 2011.

Bioavailability;
- 10 mg dose; 80-100% and is not affected by food.
- 20 mg dose; 66% in the fasted state, with food ↑ the bioavailability.

Uses; - ***Prevention* of stroke in non-valvular atrial fibrillation**.
- ***Dose***; 20 mg orally once a day.

- ***Prophylaxis* of deep vein thrombosis (DVT)** which may lead to **pulmonary embolism (PE)** ***in patients undergoing* knee or hip replacement surgery**.
  - ***Dose***;
    - ***In* DVT or PE**; ***Initial***: 15 mg orally twice a day for first 21 days of therapy. ***Maintenance***: 20 mg orally once a day for the remaining duration of treatment.
    - ***In* DVT or PE recurrence**; 20 mg orally once a day.
    - ***In* DVT prophylaxis after hip or knee replacement surgery**;
      - ***Initial***: 10 mg orally once a day starting 6 to 10 hours after surgery.
      - ***Duration of therapy***: Hip: 35 days - Knee: 12 days.

- ***Side effects***; Major side effect is **bleeding**.

- ***Contraindication***; **Patients** with **severe renal impairment** (CrCl less than 30 mL/min in DVT and CrCl less than 15 mL/min in non-valvular atrial fibrillation).

Apixaban (Eliquis®)#

Apixaban is an ***oral selective* factor Xa *inhibitor***.

- ***Uses***; - ***Prevention of* stroke in non-valvular atrial fibrillation**.
  - ***Dose***; 5 mg taken orally twice daily.
- ***Prophylaxis of* deep vein thrombosis (DVT)** which may lead to **pulmonary embolism (PE)** ***in patients undergoing* knee or hip replacement surgery**.
  - ***Dose***; ***Duration of therapy***: Hip: 35 days - Knee: 12 days.
    - ***In* DVT or PE**; 10 mg orally twice daily for the first 7 days. After 7 days, the recommended dose is 5 mg taken orally twice daily.
    - ***In* DVT or PE recurrence**; 2.5 mg taken orally twice daily after at least 6 months of treatment for DVT or PE.
    - ***In* DVT prophylaxis after hip or knee replacement surgery**; 2.5 mg taken orally twice daily, taken 12-24h after surgery.
- ***Side effects***; Major side effect is **bleeding**.

FDA warning; **Apixaban *should not be* used in the setting of lumbar puncture** or **spinal cord surgery**, ***Due to* risk of epidural or spinal hematomas**.

- ***Premature* discontinuation** of **Apixaban**, ***increases*** the **risk of thrombotic events**.

Edoxaban (Savaysa®) (Lixiana®)

Edoxaban is an ***oral selective* factor Xa *inhibitor***, it was also ***approved*** by the **FDA** in January **2015** for the ***prevention*** of **stroke** and ***non*-CNS systemic embolism**.

Uses; - ***Prevention* of stroke in non-valvular atrial fibrillation**.
  - ***Dose***; 60 mg orally once a day.
- ***Treatment* of deep vein thrombosis (DVT)** and **pulmonary embolism (PE)**.
  - ***Dose***; - >60 kg: 60 mg orally once a day.
    - ≤60 kg: 30 mg orally once a day.

FDA warning; - ***Do not* use** with **CrCL >95 mL/min**.
  - **Edoxaban *should not be* used in the setting of lumbar puncture** or **spinal cord surgery**, ***Due to* risk of epidural or spinal hematomas**.

- ***Premature* discontinuation** of **Edoxaban**, ***increases*** the **risk of thrombotic events**.
- ***Side effects***; Major side effect is **bleeding**.

Betrixaban (Bevyxxa®)

- **Betrixaban** is an ***oral selective* factor Xa *inhibitor***, it was also ***approved*** by the **FDA** in June **2017** for the ***prophylaxis*** of **venous thromboembolism (VTE)** in **adult patients *hospitalized*** for an **acute medical illness** who are at ***risk for* thromboembolic complications** due to ***moderate*** or ***severe*** *restricted* **mobility** and other ***risk factors*** for **VTE**.
- **Betrixaban** has *relatively* ***low* renal excretion** (dose adjustment only in severe renal impairment).

Factor Xa Inhibitor Antidote

Andexanet Alfa (Andexxa ®)

- **Andexanet alfa** is a ***genetically modified*** *variant* of ***human* factor Xa**.
- It is an ***antidote*** for **Rivaroxaban** and **Apixaban** (not been approved to date for Edoxaban or Betrixaban). It was approved for by US FDA in 2018.

Vitamin K Antagonists (Coumarin Anticoagulants)

Warfarin (Coumadin®)# (Marevan®)#

Warfarin ***inhibits*** **vitamin K epoxide reductase enzyme**, resulting in depletion of the reduced form of vitamin K.

Vitamin K is a ***cofactor*** for **coagulation factors** II, VII, IX, and X and anticoagulant proteins C and S is ***inhibited***.

Unlike **heparin**, the anticoagulant effects of warfarin are not observed ***immediately after drug administration***;

- ***Peak anticoagulant effect*** may be delayed **72-96 hours** (the time required to deplete the pool of circulating clotting factors).
- ***Treatment initiated*** with **UFH** or **LMWH** for the **first 5-7** days, with an overlap with **Warfarin**. Once therapeutic effects of warfarin have been established, therapy with warfarin is continued for a minimum of 3-6 months.

Uses;

- ***Prophylaxis*** and ***treatment*** of **deep vein thrombosis** (**DVT**) and its extension, **pulmonary embolism** (**PE**).
- ***Prophylaxis*** and ***treatment*** of **thromboembolic complications associated with atrial fibrillation** (**AF**) ***and/or*** **cardiac valve replacement**.
- ***Reduction*** in the **risk of death**, ***recurrent*** **myocardial infarction** (**MI**) ***and*** **thromboembolic events** such as **stroke**.
- **Protein C and S deficiency symptoms** (is an inherited disorder causes abnormal blood clotting).
- **Antiphospholipid syndrome** (is an autoimmune, hypercoagulable state caused by antiphospholipid antibodies).

- ***Dose***;
  - **International Normalized Ratio (INR)**; is the prothrombin time ratio (patient prothrombin time/mean of normal prothrombin time for lab).
  - Adjust the warfarin dose to maintain a target INR of 2.5 (INR range, 2.0-3.0) for all treatment durations.
  - ***Initial dose***: 2-5 mg orally or IV once a day for 1-2 days, then adjust dose according to results of the INR or prothrombin time (PT).
  - ***Maintenance dose***: 2-10 mg orally or IV once a day.

Color-Coded for Safety; Generic warfarin tablets may come in different shapes, but each strength comes in just one color.

- ***For example***, 5 mg tablet; peach/light orange color.

Side effects; **Hemorrhage**, **Warfarin Necrosis**, **Osteoporosis** and **Purple Toe Syndrome**.

Pregnancy; **Warfarin** is **teratogenic** and ***should never be*** **used during pregnancy**.

- ***Drug interactions***; **numerous drug interactions**.

Fibrinolytic Drugs

Fibrinolytic drugs (**Thrombolytic drug**) rapidly lyse thrombi (***dissolve* blood clots**) by catalyzing the formation of plasmin (serine protease) from its precursor plasminogen.

The ***major side effects*** of **these drugs** are **bleeding**.

These drugs are ***contraindicated*** in **pregnancy** and in ***patients with* healing wounds**, a *history of* **cerebrovascular accident, brain tumor, head trauma, intracranial bleeding** and **metastatic cancer**.

Streptokinase (SK) (Kabikinase®)#

Streptokinase is a protein synthesized by ***streptococci***.

Uses; **acute MI, DVT** and **PE**.

- ***Dose***; IV infusion of a loading dose of 250,000 units, followed by 100,000 units/h for 24-72 hours.

Streptokinase has ***high* antigenicity**, ***so* patients** with ***anti-streptococcal antibodies*** can develop **fever, allergic reactions** and **therapeutic resistance**.

- **Streptokinase** is ***rarely* used** and is no longer available in many markets.

Urokinase (Angikinase®)#

Urokinase ***also called* urokinase-type plasminogen activator (uPA)**, it is produced ***naturally*** in the body by the kidneys.

- **Therapeutic urokinase** is ***isolated*** from **cultures of human kidney cells** and has ***low* antigenicity**.
- ***Uses***; **PE, DVT, acute MI, coronary artery thrombosis** and **arterial thrombosis**.
- ***Dose***; loading; 300,000 units over 10 min. and a maintenance; 300,000 units/h for 12 hours.

Anistreplase (Eminase®)#

Anistreplase is ***also known as* anisoylated plasminogen streptokinase activator complex (APSAC)**.

It is a **complex of *purified* human plasminogen *and* bacterial streptokinase**.

- ***Uses***; **acute MI**, now this drug is discontinued in the USA.
- ***Dose***; Single IV injection of 30 units over 2 to 5 min.

Alteplase (Cathflo® Activase®)# | Reteplase (Retavase®)# | Tenecteplase (TNKase®)#

Plasminogen can also be ***activated*** endogenously by **tissue plasminogen activators (t-PAs)**.

- ***Uses***;
  - **Alteplase**; **Treatment of acute MI, massive PE** and **acute ischemic stroke**.
    - ***Dose***; IV infusion (due to very short half-life; 5-30 minutes); 60 mg over the first hour and then 40 mg at a rate of 20 mg/h.
  - **Reteplase**; **Treatment of acute MI** (***off-label used*** in **DVT** and **massive PE**).
    - ***Dose***; Double IV bolus (moderate half-life) injections of 10 units (10+10) each, separated by 30 minutes.
  - **Tenecteplase**; **Treatment of acute MI**.
    - ***Dose***; Single IV bolus (long half-life) of 0.5 mg/kg.
- ***N.B***; **Alteplase** may cause angioedema, and there may be an increased risk of this effect when combined with angiotensin-converting enzyme (ACE) inhibitors.

Antiplatelet Drugs

1) ***Inhibit*** **Thromboxane Synthesis** (**Aspirin**).
2) ***Inhibit*** **ADP-induced Platelet Aggregation** (**Clopidogrel**, **Prasugrel** and **Ticlopidne**).
3) ***Block*** **Glycoprotein IIb/IIIa Receptors** (**Abciximab**, **Tirofiban** and **Eptifibatide**).
4) **Protease-Activated Receptor-1 (PAR-1)** ***Antagonists*** (**Vorapaxar** and **Atopaxar**).
5) ***Other*** **Antiplatelet Drugs** (**Dipyridamole** and **Cilostazol**).

Thromboxane A_2 Inhibitor

Aspirin (Aspocid®)#

Aspirin ***inhibits*** **synthesis** of **thromboxane** A_2 by ***irreversible acetylation*** of **cyclooxygenase (COX) enzyme.**

Aspirin inhibit platelet function ***within*** **60 min.**

Aspirin is ***used*** in the ***prophylactic treatment*** **of transient cerebral ischemia and thromboembolic stroke**, and ***reduce*** **the incidence of recurrent MI.**

The ***recommended dose***; ranges from **75-325 mg/d.**

Side effects; **GI disturbances**, ↑ bleeding time and may cause bronchospasm in susceptible patients.

P_2Y_{12} Receptor Inhibitors

Clopidogrel (Plavix®)#	**Ticlopidine** (Ticlid®)#
Prasugrel (Effient®)#	**Ticagrelor** (Brilinta®)#

- ***Absorption*** of **Ticlopidine** ↓ **with food** ***but*** **not** with the **other agents.**

Metabolism; by the cytochrome P450 (CYP) system;

Clopidogrel is a **prodrug** that ***requires activation*** via the cytochrome P450 enzyme isoform **CYP2C19.**

Drugs that impair CYP2C19 function, such as **Omeprazole**, should be ***used with caution.***

Uses; **Myocardial infarction**, **Stroke** and **peripheral arterial disease.**

- ***Doses***; - **Clopidogrel** ***loading dose***; 300-600 mg once, ***followed*** by of 75 mg daily.
- **Prasugrel**; ***loading dose*** 60 mg ***followed*** by 10 mg daily.
- **Ticlopidine**; ***loading dose*** 500 mg ***followed*** by 250 mg twice daily, for
- **Ticagrelor**; ***loading dose*** 180 mg ***followed*** by 90 mg twice daily.

Glycoprotein IIb/IIIa Inhibitors

Abciximab (ReoPro®)#	**Eptifibatide** (Integrilin®)#	**Tirofiban** (Aggrastat®)#

Uses; These agents are **given IV**, ***along with*** **heparin** and **aspirin**, as an **adjunct to PCI** ***for the*** **prevention of cardiac ischemic complications.**

- ***Dose***; - **Abciximab**; 0.25-mg/kg IV bolus, then 0.125 mcg/kg/min. (max 10 mcg/kg) for 12 hr.
- **Eptifibatide**; 180-mcg/kg IV bolus × 2 (10 minutes apart); 2 mcg/kg/min. initiated after first bolus for 18–24 h. {maintenance dose in creatinine clearance < 50 ml/min. = 1 mcg/kg/min.}
- **Tirofiban**; 25-mcg/kg IV bolus over 3 minutes, then 0.15 mcg/kg/minute for 18–24 hr.

- ***Side effects***; The major side effects of these agents is **bleeding**, especially if used with anticoagulants.
- ***N.B***; Oral formulations of IIb/IIIa antagonists are in various stages of development.

Protease-Activated Receptor-1 (PAR-1) Antagonists

Vorapaxar (Zontivity®) | Atopaxar

- **Vorapaxar** is the ***first drug inhibit*** the **protease-activated receptor-1 (PAR-1)**, the primary receptor for thrombin, approved by the FDA in 2014.
- ***Uses***; ***reduce*** **thrombotic cardiovascular events *in patients with a history of* MI** or ***with* peripheral arterial disease**.
- ***Dose***; **2.08 mg** orally ***once-daily***, ***should be*** **used with** daily **Aspirin *and/or* Clopidogrel** according to their indications or standard of care.
- ***Side effects***; ***increases*** the **risk of bleeding**, including life-threatening and fatal bleeding.

Other Antiplatelet Drugs

Dipyridamole (Persantin®)

- **Dipyridamole** is a **vasodilator** that also ***inhibits*** **platelet function** by ***inhibiting*** **adenosine uptake**.
- ***Uses***; Dipyridamole by itself has ***little*** or ***no*** **beneficial effect**. ***Therefore***;
  - ***Used*** in **combination *primarily* with aspirin to prevent cerebrovascular ischemia** ⇨ **Aggrenox®** (aspirin/extended-release Dipyridamole capsules).
  - ***Used*** in **combination *with* warfarin *for* primary prophylaxis of thromboemboli *in patients with* prosthetic heart valves**.
- ***Side effects***; Headache and can lead to orthostatic hypotension (especially if administered IV).

Cilostazol (Pletal®)#

- **Cilostazol** is a ***newer*** **phosphodiesterase type III *inhibitor*** that ***promotes*** **vasodilation** (↑ cAMP) and ***inhibition*** of **platelet aggregation**.
- **Cilostazol** is ***extensively metabolized*** in the liver by the CYP3A4, 2C19 and 1A2 isoenzymes.
- ***Uses***; It is approved to ***reduce*** **the symptoms of intermittent claudication**.
- ***Side effects***; **Headache, GI side effects** (diarrhea, abnormal stools, dyspepsia, and abdominal pain) and **palpitation**.
- ***FDA warning***; **Cilostazol** is ***contraindicated*** in **patients with congestive heart failure**.
- ***Drug interactions***; **Itraconazole, Erythromycin, Ketoconazole, Diltiazem, Omeprazole** and **Grapefruit juice**.

Antihemorrhagic Agents

Vitamin K (konakion®)# (Amri-K®)#

Vitamins K_1 and **K_2** is a ***fat-soluble*** require bile salts for absorption from the intestinal tract.
Vitamin K_1 is ***available clinically*** in **oral** and **parenteral *forms***.
- ***Onset of effect*** is delayed for **6 hours** but the ***effect is complete*** by **24 hours**.
- ***Administration***; orally, SC, IM and IV.
- ***FDA warning***; IV administration of vitamin K_1 ***should be*** **very slowly**, not exceeding 1 mg/minute, **Severe hypersensitivity reactions**, including **anaphylactic reactions** and **deaths**.

Uses; ***Treating*** **bleeding problems** caused by low vitamin K blood levels or decreased vitamin K activity, It may also be used to **treat or prevent certain bleeding problems in newborns**.

- ***Dosage Guidelines***;

Newborns prophylaxis	0.5 - 1 mg IM within 1 hour of birth
Newborns treatment	1 mg SC or IM
Usually adult dose	2.5 mg - 10 mg
Prothrombin deficiency due to warfarin	up to 25 mg
Prothrombin deficiency due to other causes	2.5 mg - 25 mg

Aminocaproic Acid (Amicar®) | Tranexamic Acid (Kapron®)# (Cyklokapron®)

Aminocaproic acid or **Tranexamic acid** are ***antifibrinolytic drugs***.
- ***Both agents*** are **synthetic**, **orally active** and **excreted in the urine**.

Uses; - **Adjunctive therapy in haemophilia** (is a group of hereditary genetic disorders that impair the body's ability to control blood clotting).
- **Bleeding from fibrinolytic therapy**.
- **Prophylaxis for re-bleeding from intracranial aneurysms**.
- **Postsurgical GI bleeding, post-prostatectomy bleeding** and **bladder hemorrhage**.
- **Tranexamic acid**; ***used as first-line*** **nonhormonal treatment of dysfunctional uterine bleeding** (**heavy menstrual bleeding or menorrhagia**), ***dose***; 650 mg three times daily for five days during menses.

- ***Dose***;
  - **Aminocaproic acid**; ***For acute bleeding syndromes***; 5 g during the first hour of treatment, followed by a continuing rate 1 g per hour. This method of treatment would ordinarily be continued for about 8 hours or until the bleeding situation has been controlled.
  - **Tranexamic acid**; short-term use (2-8 days) ***in patients with haemophilia*** to reduce/prevent hemorrhage and reduce the need for replacement therapy during and following tooth extraction; **10 mg/kg IV 3 to 4 times daily**.
- ***Side effects***; Risk of intravascular thrombosis, hypotension, myopathy, abdominal discomfort, diarrhea, and nasal stuffiness.

Ethamsylate or Etamsylate (Dicynone®)#

Ethamsylate is a ***synthetic antihaemorrhagic*** and ***angioprotective drug*** acting on the ***first step*** of haemostasis (endothelium-platelet interaction).
- ***Uses***; - ***Prevention*** and ***treatment*** of **pre- or postsurgical capillary haemorrhages**.
  - ***Prophylaxis*** and ***control*** of **blood loss from small blood vessels**.
  - ***Control*** **heavy menstrual periods** or those who suffer from **excessive bleeding due to an intrauterine contraceptive device**.
- ***Dose***; - ***Before surgery***; 500-1000 mg, ***followed*** by 500 mg every 4-6 hours.
  - ***Usual adult dose***; 500 mg 3-4 times daily.
  - ***Usual children dose***; 250 mg 3-4 times daily.
- ***Side effects***; GIT disturbance, nausea, headache, skin rash.

Plasma Fractions

Dried Factor VIII Fraction (8Y®)

- It is a ***concentrate*** of **Factor VIII** and **von Willebrand Factor (VWF)** ***prepared from*** **blood plasma** from screened donors and then heat-treated.
- ***Uses***; IV injection, to ***prevent*** & ***treat*** **bleeding in patients with haemophilia A** (an inherited shortage of Factor VIII in the blood) or von Willebrand disease (VWD).
- ***Dose***; 10-50 IU/kg body weight, doses may be repeated at intervals of 8, 12 or 24 hours, as required.
- ***Warning***; Because this product is made from human blood, it may carry a **risk of transmitting infectious agents** and may cause **hypersensitivity** or **allergic reactions**.

Factor IX Complex (BEBULIN®)

- **BEBULIN®** is a nano-filtered and vapour heated is a purified, sterile, freeze-dried concentrate of the **coagulation factor IX** (Christmas factor) as well as **Factor II** and **Factor X** and ***low amounts*** of **Factor VII**. In addition, the product contains ***small amounts*** of **heparin**.
- ***Uses***; ***prevention*** and ***control*** of **bleeding episodes in adult patients with haemophilia B** (congenital Factor IX deficiency or Christmas disease).
- ***Dose***; (IV only) ***Minor bleeding***; 25-35 IU/kg once. ***Moderate***; 50-65 IU/kg every 24 hours twice or until adequate wound healing. ***Major***; 75-90 IU/kg every 24 hours 3-4 times or until adequate wound healing.
- ***Warning***; **Hypersensitivity** or **allergic reactions** ***may occurs***.

Anti-Inhibitor Coagulant Complex Heat Treated (Autoplex®)

- **Autoplex®** is a sterile product prepared from pooled human plasma.
- The product is standardized by its ***ability*** to **correct the clotting time** of **Factor VIII deficient plasma** or Factor VIII deficient plasma which contains ***inhibitors*** to **Factor VIII**.
- ***Uses***; ***only*** in **patients with inhibitors to Factor VIII** ***who are bleeding or undergo surgery***.
- ***Dose***; (IV only) 25-100 Hyland Factor VIII Correctional Units/kg of body weight, depending upon the severity of hemorrhage. If no hemostatic improvement is observed approximately 6 hours following the initial administration, the dosage should be repeated.
- ***Warning***; **hypersensitivity** or **allergic reactions**.

Anti-Inhibitor Coagulant Complex (FEIBA-$^{NF®}$)

- **FEIBA** (**F**actor **E**ight **I**nhibitor **B**ypass **A**ctivity); is a nano-filtered and vapour heated, is a freeze-dried sterile human plasma fraction with **Factor VIII inhibitor bypassing activity**.
- It contains Factors II, IX, and X, mainly non-activated and Factor VII mainly in the activated form. The product contains Factor VIII inhibitor bypassing activity and Prothrombin Complex Factors.
- ***Uses***; ***Control*** of **spontaneous bleeding episodes** ***or to cover*** **surgical interventions** in **haemophilia A and haemophilia B patients with inhibitors**.
- ***Dose***; (IV infusion) 50-100 Units of FEIBA^{NF}/kg/day is recommended.
- ***Warning***; **Hypersensitivity** or **thromboembolic event** or **risk of transmitting infectious agents**.

Recombinant Human Coagulation Factor VIIa (rFVIIa) (NovoSeven®)

- **NovoSeven®** is structurally similar to human plasma-derived Factor VIIa.
- ***Uses***; ***Control*** **bleeding episodes** and to ***prevent*** **excessive bleeding during surgery** in people;
  - **Inhibitors to clotting factors VIII** or **IX**.
  - **Congenital FVII deficiency**.
  - **Glanzmann's Thrombasthenia**.
- ***Dose***; 35-120 micrograms/kg (usually 90 micrograms/kg) given every two hours by bolus infusion until hemostasis is achieved, or until the treatment has been judged to be inadequate.
- ***Warning***; **thromboembolic event** ***may occurs***.

Cryoprecipitate (CRYO)

- The ***main constituents*** of **Cryoprecipitate** are **Factors VIII** and **XIII**, **von Willebrand Factor** and **Fibrinogen**.
- ***Uses***; **Haemophilia**, **von Willebrand disease** & **hypofibrinogenaemia** (low fibrinogen levels).
- ***Dose***; 1 U/5kg patient weight repeat if needed.
- ***Warning***; **Hypersensitivity** or **allergic reactions** or **risk of transmitting infectious agents**.

Antihyperlipidemic Agents

➢ Plasma Cholesterol Levels:-

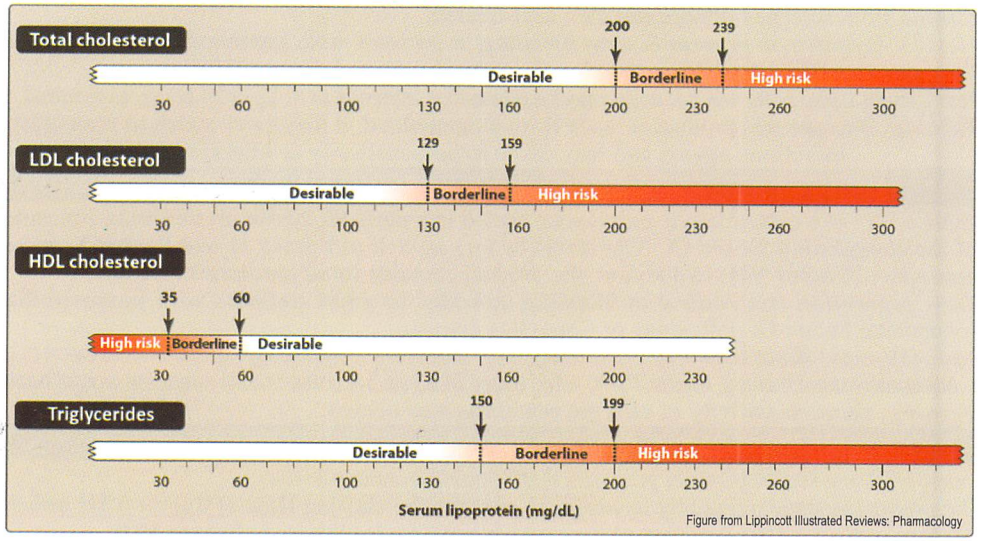


Figure from Lippincott Illustrated Reviews: Pharmacology

- **Classes of Hyperlipidemia Medications:**
  - **HMG-CoA Reductase Inhibitors (Statins).**
  - **Niacin (Nicotinic acid or Vitamin B3).**
  - **Cholesterol Absorption Inhibitors (Ezetimibe).**
  - **Bile Acid Sequestrants (Resins).**
  - **Fibric Acid Derivatives (Fibrates).**
  - **Omega-3 Fatty Acids.**

HMG-CoA Reductase Inhibitors (Statins)

Atorvastatin (Lipitor®)#		**Rosuvastatin** (Crestor®)#
Fluvastatin (Lescol® XL)		**Simvastatin** (Zocor®)#
Pravastatin (Lipostat®)	**Pitavastatin** (Lipidalon®)	**Lovastatin** (Lipdip®)

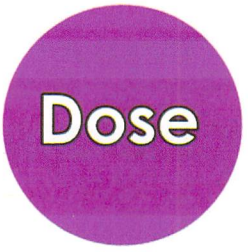
Pitavastatin, **Rosuvastatin** and **Atorvastatin** are the ***most potent LDL cholesterol lowering statins***, ***followed by*** **Simvastatin** and **Pravastatin** ***then*** **Lovastatin** and **Fluvastatin**.

Statins are useful alone or with **Resins**, **Niacin** or **Ezetimibe** in **reducing levels of LDL**.

Atoreza®; **Atorvastatin** + **Ezetimibe** # **Inegy®**; **Simvastatin** + **Ezetimibe**

Women with **hyperlipidemia** who are **pregnant**, **lactating** or likely to **become pregnant** ***should not be*** given these agents.

- Because **cholesterol synthesis** ***occurs predominantly*** **at night**, **Statins** ***except*** **Atorvastatin** and **Rosuvastatin** ***should be given*** **in the evening** if a single daily dose is used.



- ***Intensity of Statin Doses***;

High Intensity	Moderate Intensity	Lower Intensity
When taken daily, will lower LDL an average of ≥ 50%	When taken daily, will lower LDL an average of 30% to < 50%	When taken daily, will lower LDL an average of < 30%
Atorvastatin 40-80 mg Rosuvastatin 20-40 mg	Atorvastatin 10-20 mg Rosuvastatin 5-10 mg Simvastatin 20-40 mg Pravastatin 40-80 mg Lovastatin 40 mg Fluvastatin XL 80 mg Fluvastatin 40 mg twice/d Pitavastatin 2-4 mg	Simvastatin 10 mg Pravastatin 10-20 mg Lovastatin 20 mg Fluvastatin 20-40 mg Pitavastatin 1 mg

Side effects; "FDA Warning"
  # Hepatic;
    - *Elevated* liver enzymes up to 3 times normal *in* some patients.
    - *Monitoring*; liver function test; at 1–2 months, and then every 6–12 months (if stable).
  # Muscle; ######## PATIENT COUNSELLING ########
    - The *most common statin side effect* is muscle pain (10-15%).
    - *Rare reactions* statins can cause myopathy (inflammation of the muscles).
    - *Very rarely*, statins can cause life-threatening muscle damage *called* rhabdomyolysis.
    # # Coenzyme Q10 (is a cofactor for mitochondrial energy production) levels are decreased in statin use, CoQ10 supplements are sometimes used to treat statin-associated myopathy. *Dose*; 100-240 mg/daily *for up to* 2.5 years.
    # # Coenzyme Q10 (Vitamin K-like *activity*) *may affect* blood clotting, and *reduce* anticoagulant *effectiveness*.
    - Fibrates: *Increase* risk of myopathy and rhabdomyolysis.
    - Niacin: Doses greater than 1 g/day *increase* the risk.
  - Digestive; nausea, gas, diarrhea or constipation *after taking a statin*.
  - Neurological; cognitive impairment (memory loss) from statin use for several years.
  - Hormonal; *slightly* increased risk of diabetes (2-17%).
- *Pregnancy*; Category X.
- *Contraindications*; liver disease, pregnancy and lactating women.
- *Drug interaction*; *numerous* drug interaction; CYP3A4 and CYP2C9.

Bile Acid Sequestrants (Resins)

Cholestyramine (Questran®)# | **Colesevelam** (Cholestagel®) | **Colestipol** (Colestid®)

They are *anion-exchange resins* that bind negatively charged bile acids and bile salts in the small intestine; not absorbed and not metabolically altered *by the* intestine.
Cholestyramine can also relieve pruritus caused by biliary stasis.
- *Dose*; Cholestyramine are available as granular preparations;
  - *Initial dose*; 4 g orally once or twice a day.
  - *Gradual increase* to *maintenance dose*; 20 g/d is recommended.
  - *Total dosages* of 30–32 g/d may be needed for maximum effect.
  - The usual *dosage for a child* is 10-20 g/d.
  - Granular are mixed with juice/water & allowed to hydrate for 1 min.
Side effects;
  - GI disturbances;
    - Such as; Constipation, nausea and flatulence.
    - Usually *relieved by* increasing dietary fiber or mixing psyllium seed with the resin.
  - Malabsorption of fat-soluble vitamins (A, D, E and K) *may occur*.
    - *Not* used with pregnant women *due to* vitamin deficiencies that may affect the fetus.
- *Drug interaction*; *decrease* absorption of *certain* drugs.
- *Contraindications*; These agents may raise triglyceride levels and are contraindicated in patients with significant hypertriglyceridemia (≥400 mg/dL).

Niacin (Nicotinic Acid or Vitamin B3)

Niacin (Niaspan®)# (Nicotipan®)#

- Niacin or Nicotinic acid (*not* Niacinamide); is a Vitamin B_3, it is primarily *used* to treat hypercholesterolemia and pellagra (niacin deficiency).
- Niacin is *administered* orally.
- *Dose*; - *Intermediate Release*; *Initial*: 100 mg orally 3 times a day, with or after meals. *Maintenance*: 1 to 2 g orally 3 times a day, with or after meals (Max. dose 6 g/day).
  - *Extended Release* (Niaspan®); *Initial*: 500 mg orally once a day at bedtime. *Max* dose 2 g/day.
  - *Sustained Release* (Slo-Niacin®); *Initial*: 250-750 mg orally once a day morning or evening.

Skin Benefits of Niacin and Niacin Derivatives

- **Acne**; Topical 4% nicotinamide gel was as effective as 1% clindamycin gel in the treatment of moderate inflammatory acne vulgaris.
- **Lip Plumper**; Niacin is applied topically as a lip plumper, due to its vasodilation effect. The vasodilator effect on lips are slightly swollen and redder, making them appear "full-blooming" which is typically desired.
- **Moisturizing Effects**; Nicotinamide 2% cream more effective than petrolatum, the same ingredient in Vaseline, at boosting hydration levels in the patient's dry skin.
- **Rosacea Improvement**; Nicotinamide moisturizer provided substantial improvements in rosacea symptoms.
- **Possible Skin Cancer Prevention**; Oral (500 mg) nicotinamide prevent the progression of premalignant actinic keratoses to malignant squamous cell cancers.
- **Reduce Wrinkles**; Topical nicotinamide provided reductions in fine lines and wrinkles.
- **Skin Whitening**; Topical nicotinamide provided reductions hyperpigmented spots.

Side effects;

1) **Niacin Flush** (**Facial Flushing**);
   - ***Due to prostaglandin mediated vasodilation effect.***
   - > **78%** of **patients** and ***usually resolved*** **after 2 weeks** of continued therapy.
   - Flushing usually ***lasts for*** about **15** to **30 minutes**.
   - **Flushing** can be ***minimized by***;

 # # # # # # # # PATIENT COUNSELLING # # # # # # # #

1) ***Taking*** **Aspirin 325 mg** or **Ibuprofen 200 mg 30-60 minutes** ***before*** **Niacin**.
2) Use of an ***extended release*** **formulation**.
3) ***Gradual*** **dosage titration** (over 2 to 3 months).
4) ***Taking*** **Niacin** ***during*** or ***within*** **30 min.** ***after*** **meals.**
5) ***Taking*** **Niacin** at **bedtime** *with* **food** and ***avoiding*** **hot beverages, spicy foods** and **hot showers** ***around*** the **time of administration**.

2) **Upper GI Distress**; Some patients experience **nausea** and **dyspepsia** (**indigestion**).
3) **Hepatic**; ***Reversible elevations*** in **liver enzymes**; ***monitor***; every 6-12 weeks & then yearly
4) **Metabolic**; **Hyperuricemia**, **Allopurinol** can be given with niacin if needed.
   - **Hyperglycemia**, especially in obese patients, but this is usually reversible.
5) **Other**; ***Rarely***, niacin is associated with **arrhythmias**.

- ***Contraindications***; **Liver disease, severe gout** and **active peptic ulcer**.
- ***Pregnancy***; **Category C**, but not recommended.

Lactation; **Niacin** is ***excreted*** in **human milk**, may cause ***serious*** **adverse reactions** in **infants**.

Fibric Acid Derivatives (Fibrates)

Fenofibrate (Lipanthyl®)#	**Gemfibrozil** (Lopid®)#

- It is a ***pro-drug*** of the active chemical moiety **Fenofibric acid**.

Lipanthyl® Supra; is a ***film-coated*** **tablet** of ***micronized*** **Fenofibrate** and is **supra-bioavailable** (***larger*** **bioavailability**).

They are ***useful*** in ***severe*** **hypertriglyceridemia**.

They are ***useful*** in **hypertriglyceridemia** *in which* **VLDL** ***predominate***.

They also may be of ***benefit*** in ***treating*** the **hypertriglyceridemia** that ***results from treatment with*** **viral protease inhibitors**.

- ***Dose***;
  - **Fenofibrate**; is available in several formulations with several dose range and is sold under several brand names; The initial dose of tablets ranges from 40- 160 mg per day.
  - **Gemfibrozil**; 600 mg orally twice a day, 30 minutes before meal.

Side effects; **Mild GI disturbances, Gallstones, Myositis** (**Muscle inflammation;** have been reported in ***patients taking*** **Gemfibrozil** and **Statins** ***together***) and ***elevated*** **liver enzymes**.

- ***Pregnancy***; **category C**.
- ***Contraindications***: **Severe renal/hepatic disease** and **gallbladder disease**.

Cholesterol Absorption Inhibitors

Ezetimibe (Ezetrol®)

Ezetimibe is ***synergistic*** with **Statins**, ***so*** it is often ***used*** as an;
Adjunct to statin therapy. # **Statin-intolerant patients**.
- ***Dose***; - Dosage range of 5-20 mg/d. - Usually single daily dose; 10 mg/d.

Omega-3 Fatty Acids

Omega-3 Fatty Acids (Lovaza®)# (Vascepa®)# (Epanova®)#

- **Omega-3 Fatty Acids**; (ω-3 fatty acids) are **essential fatty acids**, **polyunsaturated fatty acids** (**PUFAs**) with a double bond (C=C) at the third carbon atom from the end of the carbon chain.
- **Essential fatty acids** ***inhibit*** **VLDL** and **triglyceride** ***synthesis*** in liver (unknown mechanism).
- The ***three types*** of **omega-3 fatty acids** involved ***in*** **human** physiology are **α-linolenic acid** (**ALA**) (found in plant oils), **Eicosapentaenoic acid** (**EPA**) and **Docosahexaenoic acid** (**DHA**) (both commonly found in marine oils).
- ***Efficacy*** (**DHA** and **EPA**) **Lovaza®**; ***Lowers*** TG, may ***raise*** in LDL-C.
  - **Icosapent ethyl** (**Vascepa®**); is a form of EPA, unlike other fish oil supplements, does not significantly raise LDL-C and lowers TG by 33%.

Uses; **hypertriglyceridemia** as an **adjunct *to* diet** in **adults** with **TG conc.** of **≥ 500 mg/dL**.
- ***Dose***; - **DHA** and **EPA** (**Lovaza®**); 4 g/day as a single dose or in two divided doses.
  - **Icosapent ethyl** (**Vascepa®**); 2 g twice daily with food.
- ***Side effects***; **GI effects** (abdominal pain, nausea and diarrhea) and **fishy aftertaste**.
  - **Risk of bleeding** especially in patients who are taking anticoagulant or antiplatelet drugs (***due to*** it inhibit platelet aggregation).
- ***N.B***; - **Omega-6 fatty acids**; are essential fatty acids (polyunsaturated fat).
  - **Omega-9 fatty acids**; are monounsaturated fats.
  - **Omega-3-6-9 fatty acids** play specific roles in overall health;
    # ***Prevent***; **coronary heart disease**, **stroke** and **diabetes**.
    # ***Promote***; **healthy nerve activity** and **cell development**.
    # ***Maintain*** a **healthy immune system**.
- **Omega-3-Carboxylic Acid** (**Epanova®**);
  - ***Efficacy***; ***Lowers*** TG, may ***raise*** HDL-C by 5% and may ***raise*** LDL-C by 25%.
  - ***Uses***; ***treat*** **hypertriglyceridemia** as an **adjunct *to* diet** with **TG conc.** of **≥ 500 mg/dL**.
  - ***Side effects***: ***Diarrhea***.
  - ***Dose***; 2 g or 4 g once daily.

Others

Red Yeast Rice (Cholestin®) (Statosan®)#

- **Red Yeast Rice** is ***made from*** yeast grown on rice. It is a bright reddish purple colour; ***One of these*** **ingredient *is***, **Monacolin K**, has the same structure as the drugs **Lovastatin**.
- ***Dose***; *for high cholesterol*; 1,200-2,400 mg of red yeast powder 1-2 times daily for up to 12 weeks.
- ***Side effects***: ***elevated*** **liver enzymes** and **GI symptoms**.

Garlic (Tomex®)#

- The results of research on garlic have been **mixed**, but it ***may help*** lower blood pressure, reduce blood cholesterol levels, and slow the progress of atherosclerosis. Some evidence suggests that taking garlic supplements can slightly lower blood cholesterol levels.

Drugs for Varicose Veins

- **Lifestyle Modification**; ######## **PATIENT COUNSELLING** ########

1) **Elevating the legs**; it is important to raise the legs up above the level of the heart to get the maximum effect & to do this for about a half-hour each time & during sleep.
2) ***W*eight reduction** and ***W*alking**.
3) ***Eat*** a **healthy diet** high in fiber and low in fat and salt can help.
4) ***Avoid*** **long period time** *of* **traveling**.
5) ***Avoid*** **chronic constipation, urinary retention** or **cough**.
6) ***Avoid*** **wearing tight girdles** or **belts**.
7) ***Avoid*** **alcohol**.

Compression Therapy; ***Wear*** **compression stockings** (*such as* **Venosan**® - **Duomed**®); put them in the morning before walking and before the veins become more swollen and remove them at night before going to bed. If a person tries them and experiences worsening pain, especially after walking, remove them and see a health care professional.

Venoactive Drugs

- **Venoactive drugs** (**VADs**) are a heterogenic group of drugs that has **vasoprotective effects**.
- ***They can be classified in 4 major categories***;

1) **Benzopyrones**:
   A) **α-benzopyrones**; **Coumarin**.
   B) **δ-benzopyrones**; **Diosmin**, **Micronized purified flavonoid fraction** (**MPFF**), and **Rutosides** (**Rutin**, **Troxerutin** and **Hydroxyethylrutosides**).
2) **Saponins**; **Horse chestnut seed extract** (**Aescin** or **Escin**) and ***Ruscus*** **extracts**.
3) **Other Plant Extracts**; ***Ginkgo biloba***, ***Centella asiatica***, ***Hamamelis*** and **Grape seeds** contain flavonoids, such as **anthocyanins** and **proanthocyanidins**.
4) **Synthetics Drugs**; **Calcium Dobesilate**, **Naftazone** and **Benzarone**.

Micronized Purified Flavonoid Fraction (MPFF) (Daflon®)#

- **Diosmin** and **Hesperidin** are a flavonoid, indicated for *relief* ***symptoms*** **venous insufficiency**.
- **Daflon**® formulation contain; 90% **Micronized Diosmin** + 10% **Hesperidin**.
- ***Flavonoid fractions mechanism of action*** (**Diosmin** and **Hesperidin**);

1) **Veins**; prolongs the vasoconstrictor effect of norepinephrine on the vein wall; ↑ venous tone ⇨ ↓ venous capacitance ⇨ ↑ venous return and ↓ venous hyper-pressure.
2) **Lymphatic System**; improves lymphatic drainage by ↑ frequency and intensity of lymphatic contractions and by ↑ total number of functional lymphatic capillaries.
3) **Microcirculation**; reduces capillary hyper-permeability and ↑ capillary resistance by protecting the microcirculation from damaging processes.
4) **Other**; reduces the expression of endothelial adhesion molecules and inhibits the adhesion, migration, and activation of leukocytes at the capillary level ⇨ reduction in the release of inflammatory mediators, principally oxygen free radicals and prostaglandins.

- ***Uses***; 1) ***Symptoms of*** **chronic venous insufficiency** (**CVI**);
  - ***Dose***; 500 mg 2 times daily (morning and evening) *OR* 1000 mg once daily (morning) during meals at least 6 months.

2) ***Symptoms related to*** **venous insufficiency of the hemorrhoidal plexus**.
  - ***Dose***; ***In acute hemorrhoidal crisis***; 6 tablets 500 mg (or 3 tablets 1000 mg) per day for the first 4 days and then 4 tablets 500 mg (or 2 tablets 1000 mg) a day for 3 days and then 2 tablets 500 mg (or 1 tablets 1000 mg) a day for at least 3 months.

3) ***Symptoms of*** **pre/post-operative saphenectomy** (remove large varicose veins);
  - ***Dose***; 500 mg 2 times daily (morning and evening) *OR* 1000 mg once daily (morning) during meals at least 4 weeks.

4) *Symptoms of* **postoperative hemorrhoidectomy** (surgery to remove hemorrhoids);
   - ***Dose***; 6 tablets 500 mg (or 3 tablets 1000 mg) per day for 3 days and then 4 tablets 500 mg (or 2 tablets 1000 mg) a day for 4 days and then 2 tablets 500 mg (or 1 tablets 1000 mg) a day for at least 1 week.

5) **Chronic pelvic pain** ***associated with*** **pelvic congestion syndrome**;
   - ***Dose***; 500 mg 2 times daily (morning and evening) *OR* 1000 mg once daily (morning) during meals at least 4 to 6 months.

- ***Side effects***; Diarrhea, dyspepsia, nausea and vomiting.
- **Daflon**®; is considered to be ***safe*** during **pregnancy** and **breastfeeding**.

Rutin (Ruta-C®)#

- **Rutosides** such as **Rutin** are herbal remedy which have been shown to ***reduce*** swelling and skin changes in other conditions affecting the veins such as in **chronic venous insufficiency (CVI)**.
- Rutin is an **antioxidant**, **anti-inflammatory**, **antithrombotic**, **cytoprotective** and **vasoprotective**.
- **Vitamin C** ***increases*** **rutin effects** and has a ***positive*** **effect** on **lipids metabolism**.
- The greatest benefits of rutin are in ***treating*** **varicose veins** and **hemorrhoids**.
- ***Dose***; 500 mg of rutin per day.

Aescin or Escin (Reparil®)#

- **Aescin** or **Escin** is a mixture of saponins with **anti-inflammatory**, **vasoconstrictor** and **vasoprotective** effects.
- ***Effect***; Antiedematous and anti-inflammatory effect.
- ***Uses***; Oral horse chestnut seed extract (**Aescin**) is effective in the short-term treatment of mild to moderate long-term **venous insufficiency**.
- **Aescin** 20-120 mg is available in tablet form and topical gels containing aescin 2% are available.
- ***Dose*** of **Reparil**® tablets; 20-40 mg 3 times daily with a little fluid after meals.
- Most commonly ***side effects***; nausea and stomach discomfort.

Oligomeric Proanthocyanidin Complex (OPC) (Gervital®) (Grapexon®)

- **OPC** are ***effective*** against; **Venous insufficiency** (**varicose veins**), **atherosclerosis**, **night vision** and **attention deficit hyperactivity disorder** (**ADHD**).
- Usual adult ***dose*** in **varicose veins**; 150 mg daily.

Calcium Dobesilate (Doxium®)#

- **Calcium Dobesilate** is a calcium salt of **Dobesilic acid**.
- It is commonly ***used*** in the treatment of **diabetic retinopathy** and **chronic venous insufficiency**.
- It acts on the capillary walls by regulating its impaired physiological functions of resistance and permeability, it reduces plasma and blood hyper-viscosity.
- ***Usual adult dose***; 500-1000 mg once or twice a day with the main meals.

Other Agents

Pentoxifylline (Trental®)#

Pentoxifylline is a **methyl-xanthine** *derivative* that ***inhibits*** **phosphodiesterase** enzyme and ***affects*** **blood rheology**.
- It improves blood flow by increasing erythrocyte and leukocyte flexibility. It also inhibits platelet aggregation.
- ***Mechanism of action***; It inhibits erythrocyte phosphodiesterase, resulting in an increase in erythrocyte cAMP activity ⇨ erythrocyte membrane becomes more resistant to deformity. Along with erythrocyte activity, it also decreases blood viscosity by reducing plasma fibrinogen concentrations and increasing fibrinolytic activity. It is also a non-selective adenosine receptor antagonist.
- It is ***used*** in the treatment of **peripheral vascular diseases** and in the **management of cerebrovascular insufficiency**.
- It is ***used*** in **intermittent claudication** due to chronic occlusive arterial disease of limbs.
- It is ***also effective*** in **venous ulcer** with compression therapy.
- ***Dose***; 400 mg orally 3 times a day.

Drugs for Hemorroides

Lifestyle with Home Remedies;

Patient Counselling # #

Topical treatments; apply an **OTC hemorrhoid cream** or **suppository** containing **hydrocortisone** or use pads containing witch-hazel (astringent plant extract) or a numbing agent such as **Preparation H®** cream, suppository, totables or wipes.

Sitz bath; by soaking anal area in plain warm water 10 to 15 min. two to three times a day.

Keep the anal area clean; by shower daily. Avoid soap, it may aggravate the problem. Avoid alcohol based or perfumed wipes.

Don't use dry toilet paper; keep the anal area clean after a bowel movement and use moist towelettes or wet toilet paper that doesn't contain perfume or alcohol.

Apply cold; apply ice packs or cold compresses on the anus to relieve swelling.

Take oral pain relievers; such as short-term use of NSAIDs.

Medications

Topical (or **suppository**) **corticosteroids**; relieve inflammation and itching (should not be used for more than 2 weeks, because they can thin the skin).

Topical zinc oxide, **petroleum jelly**, **cocoa butter**, **hard fat**, **mineral oil** or **shark liver oil**; can prevent further injury and reduce itching by forming a barrier over hemorrhoids.

Topical local anesthetic; can help some people, especially those who have painful external hemorrhoids.

Topical Nitroglycerine and **Diltiazem**; also have been used to relieve symptoms associated with anal sphincter spasm.

Topical vasoconstrictor (**Phenylephrine**) or **astringent** (**Witch-hazel**); reduce pain associated with hemorrhoids by contract swollen veins.

 # Preparation H® #

- Preparation H® was originally developed since 1935. The H simply for "Hemorrhoid".
- Preparation H® which became one of the world's best-selling hemorrhoid treatments.
- The product is sold and manufactured by Pfizer since 2009.
- It is available in several formulation such as; cream, suppository, totables or wipes.
- It contains medications such as that are discussed above.

- **Oral Venoactive Drugs** such as **MPFF** (**Daflon®**).
- **Oral NSAIDs**; relieve pain (should not be used for more than 1 week).

Procedures

A) Office-based Procedures;

1) **Rubber Band Ligation (RBL).**
2) **Sclerotherapy** and **Cryotherapy.**
3) **Coagulation (infrared, laser** or **bipolar).**

2) Surgical Procedures;

1) **Excisional Hemorrhoidectomy.**
2) **Stapled Hemorrhoidectomy (SH).**
3) **Transanal Hemorrhoidal Dearterialization (THD).**

Central Nervous System (CNS)

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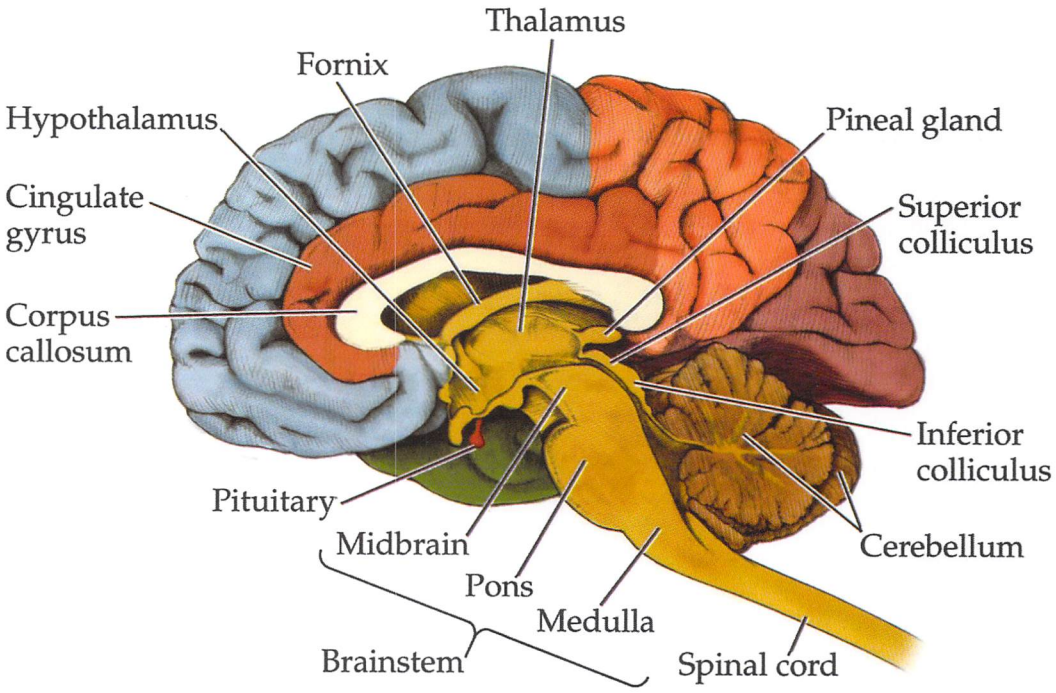

Sedative-Hypnotic Drugs

I) Benzodiazepines (BDZs)

➢ **Classification and *examples*:-**

Long-acting (> 24 hrs. half-life)		
Diazepam (Valium®)#	**Clonazepam** (Rivotril®)#	**Clorazepate** (Tranxene®)
Quazepam (Doral®)	**Flurazepam** (Dalmane®)	**Clobazam** (Frisium®)
Intermediate-acting (12-24 hrs. half-life)		
Bromazepam (Calmepam®)	**Lorazepam** (Ativan®)	**Estazolam** (ProSom®)
Chlordiazepoxide (librium®)	**Temazepam** (Restoril®)#	
Short-acting (< 12 hrs. half-life)		
Alprazolam (Xanax®)#	**Midazolam** (Dormicum®)#	**Oxazepam** (Comedormir®)
Triazolam (Halcion®)		

** ***All*** **benzodiazepines** are **sedating** (***anxiolytic***), ***but*** only ***five*** benzodiazepines are FDA approved as **sedative-hypnotics** *because* they are rapidly absorbed and produce CNS sedation more quickly;

5 BDZs Hypnotics

- ***Long-acting***; **Quazepam** and **Flurazepam**.
- ***Intermediate-acting***; **Temazepam** and **Estazolam**.
- ***Short-acting***; **Triazolam**.

BDZs Mechanism of Action; **1) BDZs *potentiate*** the **action** *of* **GABA** by binding to BDZs sites (BZ_1 or BZ_2) on $GABA_A$ receptors ⇨ ***increasing*** their **affinity** *for* **GABA. 2)** This ***results*** in an ***increased*** **opening** of **Cl^- channels** and ***enhanced*** **hyperpolarization** ⇨ sedative effect.

All **BDZs *exhibit five therapeutic* properties**;

1) **Anxiolytic** (*also known as* **minor tranquilizers**); ***At low doses***.
2) **Hypnotic**; ***At high doses*** have hypnotic effects.
3) **Amnesic Actions** (*memory loss*); ***All*** **BDZs** cause ***temporary*** **impairment of memory**.
4) **Anticonvulsant**; ***Several*** **BDZs** have **anticonvulsant activity**.
5) **Muscle Relaxant**; ***At high doses***, ***several*** **BDZs *relax*** the ***spastic*** **skeletal muscle**.

Uses;

1) **Anxiety Disorders**; ***The most commonly prescribed***; **Clonazepam, Chlordiazepoxide, Lorazepam, Diazepam** and **Alprazolam**.
2) **Sleep Disorders**; ***The most commonly prescribed BDZs as sedative-hypnotics***; **Quazepam, Flurazepam, Temazepam, Estazolam** and **Triazolam**; ***newer hypnotics***; **Zolpidem, Zaleplon** and **Eszopiclone *more* preferred**.
   * People with **problems** in ***sleep initiation***; most likely benefit from an agent with a quick onset.
   * People with **problems** in ***sleep maintenance***; most likely benefit from an agent with a longer half-life.
3) **Adjuncts to Anesthesia**; ***shorter-acting agents*** (**Midazolam**) are often ***used to*** **facilitate amnesia** in anxiety-provoking procedures, such as endoscopy, dental procedures and angioplasty. **Diazepam, Lorazepam** & **Midazolam** are used *IV* in **anesthesia**.
4) **Seizures**; In a **hospital emergencies**; **IV Clonazepam** (*stronger*), **Lorazepam** (*longer*) and **Diazepam** (*faster*) are ***first-choices***. **Clobazam** is ***widely used*** by ***specialist*** **epilepsy clinics** ***worldwide***, while **Clonazepam** is ***most*** **popular**.
5) **Alcohol Withdrawal Syndrome**; **Chlordiazepoxide** (*most commonly*), **Clorazepate, Diazepam, Lorazepam**, and **Oxazepam** are the ***preferred choice*** to ***reduce*** the **risk** of **withdrawal-related seizures**.
6) **Muscle Spasms**; **Diazepam** is ***useful*** in the treatment of skeletal muscle spasms.

Side effects;
Next day **drowsiness** and **confusion** (***most common side effects***);
- *Most* common with ***long-acting as*** **Diazepam** & **Flurazepam**.
Next day **sedation**, **ataxia** and **impair driving**; *Most* common in elderly.
Cognitive Impairment (**Anterograde Amnesia**);
- ***All*** BDZs with ***long-term*** **use** appear to ***impair ability*** to learn new information and may also impair memory storage and recall.
Hypotension & **Respiratory Depression**;
- **IV** BDZs can be associated with cardiac and/or respiratory arrest.
Rebound Insomnia;
- Can occur when the drug is discontinued abruptly and usually lasts for 1-2 days It is most common after the use of short acting agents (*most common with*; **Triazolam**).
Tolerance, **Dependence** and **Abuse**;

 # # # # Tolerance # # # #

It is occurs when used for more than **1-2 weeks**.
It is ***associated with*** a decrease in **GABA receptor density**.
Cross-tolerance exists between the **BDZs** and **Ethanol**.
Triazolam often shows a ***rapid development*** of tolerance.

 # # # # Dependence and Abuse # # # #

Dependence occurs within weeks to months of continued use.
Abrupt **cessation** can ***lead to withdrawal symptoms***; **Confusion**, **anxiety**, **agitation**, **restlessness**, **insomnia**, **tension** and (*rarely*) **seizures**.
Short-acting **BDZs**, such as **Triazolam**, more abrupt and ***severe*** **withdrawal reactions**.

- ***Notes***; - ***Pregnancy***; **Sedative-hypnotics** may ***increase*** the **risk** of **fetal malformations**.
- **Alcohol** & *other* **CNS depressants** ↑ sedative–hypnotic effects of BDZs.
- ***Most*** **sedative-hypnotics** ***used with caution*** in patients with **renal** or **hepatic disease**.
- **BDZs** should be ***avoided*** in patients with acute **closed-angle glaucoma**.
- **Flumazenil** (BDZs antagonist) used in BDZs overdoses.

Flumazenil (Anexate®)#

Flumazenil ***rapidly reverses*** the **effects of BDZs** by ***competitive*** **inhibition** at the **BDZs binding site** on the **$GABA_A$ receptor**.
It is primarily ***used*** to treat **benzodiazepine overdoses**.
The drug is available for **IV** **administration** ***only***.
Onset is ***rapid*** (within 1-2 min.), ***but*** the ***duration*** is ***short***, with a half-life of about 1 hour, so, ***frequent administration*** may be **necessary** to ***maintain*** **reversal** of a **long-acting BDZs**.
Dose; 0.2 mg IV one time over 30 seconds ⇨ if no response after 30 seconds ⇨ repeated 0.5 mg every minute (maximum 3 mg/hr).
- ***Common side effects***; dizziness, nausea, vomiting and agitation.

Non-Benzodiazepines

Zolpidem (Stilnox®)# (Zodium®)#	**Zaleplon** (Siesta®)# (Sleep-aid®)#
Eszopiclone (Lunesta®)# (Night Calm®)#	**Zopiclone** (Hypnor®)#

They are an ***oral*** **non-benzodiazepine hypnotics**, are also known as **Z-drugs**.
Eszopiclone is the active ***dextrorotatory*** stereoisomer of **Zopiclone**
Compared with BDZs; ***More*** selective as hypnotics agent, ***Lower*** risk of tolerance and withdrawal, ***No*** significantly alter the various **sleep stages**, ***No*** **anticonvulsant** or **muscle-relaxing** properties, ***No*** **respiratory depressant** effect.
- **Zolpidem** is available as an IR, CR, sublingual tablet (**Edluar**®) and sublingual spray (**Zolpimist**®), the FDA has ***reduced*** the **dosing** to ***limit*** **next day impairment**.
- **Zaleplon** is indicated only for short-term treatment of insomnia (*duration*; 3 h.).
Uses; **insomnia treatment**;
- **Zaleplon** is ***indicated only*** for **short-term treatment of insomnia**.
- **Zolpidem** (SR) and **Eszopiclone** can be used for **chronic insomnia**.

#***Side Effects***; **Nightmares**, **agitation**, **anterograde amnesia**, **headache** & **daytime drowsiness**.
- This drugs are classified as a Schedule IV controlled substance by federal U.S. drug policy.

II) Barbiturates

Barbiturates, were be used as **anxiolytic-hypnotic** ***in the past***, but **today** they have been ***largely replaced*** by the **benzodiazepines**, ***because***;

BDZs are	**1)** High therapeutic index. **2)** More selective. **3)** Mild physical dependence and tolerance. **4)** Little cardiovascular and respiratory depression. **5)** Not significantly enzyme inducer. **6)** Available of specific antidote (**Flumazenil**).

➢ Classification and *examples*:-

Long-acting		
Phenobarbital or Phenobarbitone (Luminal®)#		
Intermediate-short-acting		
Secobarbital (Seconal®)#	**Amobarbital** (Amytal®)#	**Butalbital** (Fioricet®)
Ultra-short-acting		
Thiopental (Pentothal®)#		

- **Phenobarbital** has a **duration of action** ***greater than*** a **day (1-2 days)**.
- **Secobarbital**, **Amobarbital** & **Butalbital** have a **duration of action** ***less than*** a **day (3-8 hr)**.
- **Thiopental** ***acts within*** **seconds** and has a ***duration of action*** of about **20 min**.

Pharmacological Action;

1) CNS Depression;
- ***At low doses***; **Sedation**. - ***At normal doses***; **Anxiolytic** and **anticonvulsant effects**.
- ***At higher doses***; **Hypnosis**, ***followed by*** **anesthesia** and finally **coma** and **death**.

2) CVS Depression;
- ***At low doses***; Minimal effects. - ***At higher doses***; **Hypotension**.

3) Respiratory Depression;
- ***Lethal doses***; **Respiratory depression** and **death**.
- ***The Lethal Injection***; **Sodium Thiopental**, as an **anesthetic** agent (unconscious in less than 30 seconds) and *facilitate* **respiratory depression**.

4) Liver Microsomal Enzyme Inducers; most notably CYP2C9, CYP2C19 and CYP3A4.

Uses;

1) Anesthesia; **Thiopental** have been used IV to **induce anesthesia**.

2) Sedative-hypnotic; ***now*** **rarely** (or not) used.

3) Seizures; **Phenobarbital** has ***specific*** **anticonvulsant activity** (**tonic-clonic seizures**), ***first-line choice*** of **neonatal seizures**

- **Fioricet®**; **Butalbital** is ***commonly*** **used** in ***combination with*** **Acetaminophen** and **Caffeine** or **Aspirin** and **Caffeine** as a sedative to assist in the management of **tension-headache** or **migraine headache**.

Side effects; - **Drowsiness**, **confusion** and **impaired concentration** (most common).
- ***CNS depressant effects*** of **barbiturates** ***synergize*** with ***other*** **CNS depressants**.
- **Hypersensitivity**: facial edema and skin rash (1 to 2%).
- **Death** may also result from overdose (CV and respiratory depression).
- ***Withdrawal Symptoms***; withdrawal is ***much more severe*** than that associated with opiates and ***can result*** in **death**. ***Abrupt cessation*** of barbiturates after chronic administration may cause tremors, anxiety, nausea, vomiting, seizures and cardiac arrest. ***Treatment of phenobarbital overdose*** is **supportive** (***no*** **antidote available**).
- **Tolerance**, **psychological** & **physical dependence** may occur with continued use.

- ***Drug Interactions***; such as phenytoin, oral contraceptives and most oral anticoagulants.
- **Barbiturates** ***contraindicated*** in **pregnancy**, it can depress the fetus.

III) Other Agents

Non-Barbiturates

Chloral Hydrate (Chloral®)#

Chloral Hydrate is a **non-barbiturate sedative-hypnotic**.
- **Hypnotic effects** of chloral hydrate due to its ***active metabolite*** **Trichloroethanol**.
Onset of Action; 30-60 minutes.
Uses; - **Short-term insomnia**, it is also still used as a ***sedative prior*** to EEG.
- **Prevention of alcohol withdrawal symptoms**.
- **Relieve anxiety *due to* certain procedures** (minor medical or dental).
- ***Dose***; **Adult**; 500 mg to 1 g 15 to 30 min before bedtime [every 6 h, if needed (max, 2 g/day)].
Child; 50 mg/ kg of body weight.
- ***Most Common Side Effects***; **Ataxia**; **dizziness**, **rashes** and **gastric discomfort**.

Serotonin Agonists

Buspirone (Buspar®)#

Buspirone is a ***selective*** **5-HT_{1A} agonist**, which is an **antianxiety agent**.
It is primarily ***used*** to treat **generalized anxiety disorder (GAD)**;
- ***Contraindication***: should ***not*** be used with **MAOIs** may cause **serotonin syndrome**.
- ***Most common side effects***: dizziness, nausea, headache, nervousness, and excitement.
- ***Usual*** **adult** ***dose***: - ***Initial***: 5 mg 3 times a day. - ***Maintenance***: 20 to 60 mg/day in divided doses.
- **Buspirone** has ***no*** potential for **abuse** and ***no*** evidence of dependence or withdrawal effects.

Melatonin Agonists

Ramelteon (Rozerem®)#

Ramelteon is ***first*** in a **new class** of sleep agents that ***selective*** **agonist** at the **MT_1** and **MT_2** subtypes of **melatonin receptors**. - ***Duration of Action***; 2-5 hours.
- ***Metabolism***; primarily by CYP 1A2, ***but*** affect by 2C9 and 3A4 inducers or inhibitors.
Used; ***long term*** for **chronic insomnia**, ***particularly*** in **sleep initiation**.
- ***Dose***; 8 mg orally within 30 minutes of going to bed. (Maximum dose: 8 mg per day).
- ***Common Side Effects***; dizziness, fatigue, somnolence and may also increase prolactin levels.
- ***To date***; it has ***minimal*** potential for abuse, ***no*** evidence of dependence or withdrawal effects.

Orexin Antagonists

Suvorexant (Belsomra®)#

Suvorexant is a ***selective***, dual **orexin receptor antagonist** (**OX_1** and **OX_2**).
- It was approved by the FDA on 2014 and became available in US in February 2015.
Uses; **Insomnia**, ***characterized by*** **difficulties** with **sleep initiation** and/or **sleep maintenance**.
- It is ***metabolized*** by CYP 3A4 (affect by 3A4 inducers or inhibitors).
- This drug is ***classified as*** a Schedule IV controlled substance by federal U.S. drug policy.

Antihistamines

Doxylamine (Donormyl®)#

OTC ***First*** **generation antihistamines** with ***sedating properties***, such as **Doxylamine** and **Diphenhydramine** are effective in ***treating*** **mild types** of **situational insomnia**, ***but not*** as effective as BDZs or non-BDZs. - ***Side effects***; **anticholinergic effects**.

Antidepressants

Doxepin (Silenor®)#

Management of insomnia, ***particularly*** in **patients *with* difficulty sleep maintenance**.

Herbal Agents

Valerian Extracts (Dormival®)# | **Kava-Kava** | ***Humulus lupulus*** **(hops) extract**

Antidepressant Drugs

I) Tricyclic Antidepressants (TCAs)

Tertiary Amines		
Imipramine (Tofranil®)#	**Amitriptyline** (Tryptizol®)#	**Clomipramine** (Anafranil®)#
Trimipramine (Surmontil®)#	**Doxepin** (Silenor®)#	
Secondary Amines		
Desipramine (Norpramin®)	**Nortriptyline** (Pamelor®)	**Protriptyline** (Vivactil®)
Tetracyclic Antidepressant		
Maprotiline (ludiomil®)	**Amoxapine** (Amokisan®)	

Tricyclic antidepressants (**TCAs**) were the ***first*** **antidepressants available**.
- Also in the **1950s** the ***first*** **tricyclic antidepressants** (**Imipramine**) were discovered.
They are ***used for*** **depression**, but they have ***several*** **off-label uses** such as treatment for **pain syndromes**, **migraine prophylaxis** and **anxiety disorders**.
- They are ***effective***, ***but*** **adverse effects** have ***limited*** **their use**.
- The TCAs were the ***dominant*** class of antidepressants ***until*** the introduction of **Selective Serotonin Reuptake Inhibitors** (**SSRIs**) in the **1980s** and **1990s**.
- **TCAs** have ***long*** **half-lives**; most are ***dosed*** **once daily** at **night** ***because*** **sedating effects**.
TCAs have a ***narrow*** **therapeutic index** (five- to six-fold the maximal daily dose of **imipramine** can be lethal), ***increasing*** their probability for **toxicity**, ***monitoring*** **serum concentration** during therapy ***may needed***.
Mechanism; **TCAs** ***inhibits*** **neuronal reuptake** of **NE** and **5-HT** into ***presynaptic*** nerve terminal ⇨ ***increase*** **concentration** of **monoamine** in **synaptic cleft**.
- **TCAs** ***elevate*** **mood**, ***improve*** **mental alertness** and ***increase*** **physical activity**.
- The ***onset*** of the **mood elevation** is **slow**, requiring **2 weeks** or **longer**.
- ***After*** a **therapeutic response**, the **dosage** can be ***gradually*** **reduced** to ***improve*** **tolerability**, unless **relapse** occurs.
Uses; - **Management of moderate** to **severe depression**.
- **Panic disorder**.
- **Imipramine** has been used to ***control*** **bed-wetting** in **children** ***older than*** **6 years** of age; but now, it has ***largely*** been *replaced by* **Desmopressin** (***vasopressin analogue***).
- **Amitriptyline**, have been used to help ***prevent*** **migraine headache**.
- **Doxepin**; *low doses* of doxepin can be used to ***treat*** **insomnia**.
- **Clomipramine**, has been used to ***delay ejaculation*** in **premature ejaculation**; but now, it has largely been replaced by **SSRIs**.
- ***Several*** **TCAs**, including **Amitriptyline**, **Nortriptyline**, **Desipramine**, and **Imipramine**, have been studied for ***treatment*** of **neuropathic pain**.

Side effects;
- **Muscarinic Receptors Blocking Side Effects** (**Atropine** ***like action***).
- **α-adrenergic Receptors Blocking Side Effects**; **Orthostatic hypotension**.
- **Histaminic (H_1) Receptors Blocking Side Effects**; **Sedation**.
- **Serotonergic Receptors Blocking Side Effects**; **Weight gain** and **sexual dysfunction**.
- **Quinidine Like Effects** (**Sodium Channel Blockers**); **life-threatening arrhythmias**.

Drug interactions; **Warfarin**, **Aspirin**, **LME inhibitors** or **inducers**, **Clonidine**, **Quinidine**, **MAOIs** and **SSRIs**.
- ***Contraindications***; **Benign prostatic hyperplasia**, **urinary tension**, **glaucoma** and **epilepsy**.
- **Life-threatening arrhythmias of TCAs** *are treated by*; **Sodium bicarbonate**.
The **US FDA** requires ***all*** **antidepressants**, to carry a **black box warning** with a generic warning about a ***possible*** **suicide risk**.

II) Selective Serotonin Reuptake Inhibitors (SSRIs)

- ***Advantage***; **SSRIs** have ***little blocking*** activity at **muscarinic**, **α-adrenergic**, and **histaminic H_1 receptors**. ***Therefore***, **common side effects** *associated with* **TCAs**, are ***not commonly*** **seen** with the **SSRIs**. **SSRIs** have ***largely replaced*** **TCAs** and as the ***drugs of choice*** in **depression**.
- The **FDA** has ***approved*** **six SSRIs** for the treatment of **depression**:

Fluoxetine (Prozac®)#	**Sertraline** (Lustral®)#
Paroxetine (Seroxat®)#	**Fluvoxamine** (Faverin®)#
Citalopram (Cipram®)#	**Escitalopram** (Cipralex®)#

Escitalopram is the ***pure*** **S-enantiomer** of **Citalopram**.
Fluvoxamine is ***indicated only*** for **obsessive-compulsive disorder** (**OCD**) but is an **antidepressant**.
- ***All*** **SSRIs** are ***well*** **absorbed** after ***oral*** **administration**.
- **Food** has ***little*** **effect** on absorption (***except***, **Sertraline**; **↑ absorption**).
Fluoxetine ***differs*** from the ***other*** **SSRIs**; It having a ***much*** **longer half-life**, ***due to*** it **active metabolite** **Norfluoxetine**, The ***elimination*** **half-life** of **Norfluoxetine** is about ***three*** **times** longer than **fluoxetine**. **Fluoxetine** has to be ***discontinued*** **4 weeks** or **longer** ***before*** an **MAOI** can be administered to ***decrease*** the **risk** of **serotonin syndrome**.

	Half-life	Active metabolite	Usual dose (mg/day)	Maximal daily dose (mg)
Fluoxetine	1-4 days	**Norfluoxetine**	20-60	80
Sertraline	26 hours	No	50-200	200
Paroxetine	21 hours	No	10-60	50-60
Fluvoxamine	15 hours	No	50-300	300
Citalopram	32 hours	No	20-40	40
Escitalopram	27-32 hours	No	10-20	20

Extended formulations: **Fluoxetine** **90 mg** (**Durazac®**) can be taken ***once*** **weekly**.
Escitalopram is ***S-isomer*** of **Citalopram**; **10mg** **Escitalopram** is as ***effective as*** **20 mg** **Citalopram**.
- ***Metabolism*** by **cytochrome P450** enzymes;
  - **Fluoxetine** and **Paroxetine** are potent inhibitors of the CYP2D6.
  - **Fluvoxamine** is an inhibitor of CYP3A4.
  - **Citalopram**, **Escitalopram** & **Sertraline**; modest CYP interactions.
- The ***efficacy*** of **SSRIs** is **equal** for **treatment** of **depression**.
- ***Onset*** & ***duration***; **SSRIs** (***Other*** **Antidepressants**), typically take at ***least*** **2 weeks** to ***produce*** **significant improvement** in **mood** and ***maximum*** benefit may require up to **12 weeks** or **more**.
Uses; - **Depression**; All SSRIs ***except*** **Fluvoxamine** (***but*** it is effective).
  - **Generalized Anxiety Disorder** (**GAD**); All SSRIs ***except*** **Fluvoxamine**.
  - **Obsessive Compulsive Disorder**; All SSRIs.
  - **Eating Disorders** (**Bulimia Nervosa**); ***only***, **Fluoxetine**.
  - **Stroke Recovery** All SSRIs ***except*** **Fluvoxamine**.
  - **Premature Ejaculation**. All SSRIs (*include*; **Dapoxetine**) ***except*** **Fluvoxamine**.
Side effects; **SSRIs** are considered to have ***fewer*** or ***less*** **severe adverse effects** than the **TCAs** and **MAOIs**, ***but not without*** **adverse effects**.
  - ***In general***; **side effects of SSRI**; **GI side effects** (nausea, vomiting and diarrhea), **headache**, **anxiety**, **agitation**, **fatigue**, **sexual dysfunction**, **changes in weight** and **sleep disturbances**.

Sexual Dysfunction; may include ***loss*** of **libido** and ***delayed*** **ejaculation**.

- ***Treatment of SSRI-induced sexual dysfunction***;

1) ***Adding*** **Bupropion**, or
2) ***Lowering*** the dose of the **SSRI**, or
3) ***Adding*** an agent such as **Sildenafil** or **Cyproheptadine**, or
4) ***Changing*** to a drug less likely to cause this problem.

Citalopram **40 mg** ***increase*** the **risk** of **QT interval** ***prolongation***.

Serotonin Syndrome; ######## PATIENT COUNSELLING

- Because these drugs have ***potent*** **serotonergic activity**, **combinations** with ***other drugs*** **affecting serotonin** can ***lead to*** **serotonin syndrome**.
- ***Other drug*** **examples**; **MAOIs**, **TCAs**, **SNRIs**, **Dextromethorphan**, **Meperidine**, **Sympathomimetics**, **Triptans** and **Lithium**.

Serotonin syndrome ***includes***;

1) **Neuromuscular hyperactivity**; Muscle rigidity, tremors & incoordination.
2) **Altered mental status**; Agitation, confusion and hypomania.
3) **Autonomic instability**; Hyperthermia and diaphoresis.

Treatments; - ***Discontinuing*** the **offending agent**.

Supportive treatments *such as* **cooling blankets** and **respiratory assistance** and ***providing*** **Clonazepam** ***for*** **seizures** and **Nifedipine** ***for*** **hypertension**.

Withdrawal Symptoms; ######## PATIENT COUNSELLING

Sudden **discontinuation** of **short half-life** **SSRIs** such as **Paroxetine** and **Sertraline** is associated with a ***discontinuation syndrome*** in some patients ***characterized by***;

- Dizziness, malaise, and flu-like symptoms, agitation and irritability, nervousness and changes in sleep pattern.

- *Symptoms* ***beginning*** 1 or 2 days after stopping the drug and persisting for 1 wk or longer.
- ***So*** a ***gradual dose reduction*** (e.g., over 2-4 weeks) may be indicated.
- **Fluoxetine** has the lowest risk of causing an SSRI withdrawal syndrome.

- ***Pregnancy***; ***Most*** **antidepressants** are **category C** (**Paroxetine** is a **category D**).
- ***Children***; Antidepressants should be used cautiously in children.
  - **Fluoxetine**, **Sertraline** and **Fluvoxamine** are ***approved for*** use in ***children*** to treat **obsessive-compulsive disorder**.
  - **Fluoxetine** and **Escitalopram** are ***approved*** to treat ***childhood*** **depression**.

III) Serotonin/Norepinephrine Reuptake Inhibitors (SNRIs)

- **SNRIs** ***inhibit*** the **reuptake** of **serotonin** and **norepinephrine** into the presynaptic neuron.

SNRIs, ***may be*** **effective** in **depression** in ***patients in whom*** **SSRIs** are ***ineffective***.

SNRIs, ***may be*** **effective** in **depression** is often ***accompanied*** by ***chronic*** **painful symptoms**, such as **backache** and **muscle aches** (This pain is, in part, modulated by serotonin and norepinephrine pathways in the CNS).

Both **SNRIs** and **TCAs**, are **effective** in ***relieving*** **pain** ***associated with*** **diabetic peripheral neuropathy**, **postherpetic neuralgia**, **fibromyalgia** and **low back pain**.

The **SNRIs** have ***relatively fewer*** **CYP450 interactions** ***than*** the **SSRIs**.

All the **SNRIs** may ***produce*** **serotonin syndrome**.

SNRIs ***may produce*** a **withdrawal syndrome** ***if*** treatment is ***abruptly*** **stopped**.

Both **Duloxetine** and **Venlafaxine** have been ***associated*** with ***higher rates*** of **suicide** compared with **SSRIs**. The ***risk of*** **suicide** with **SNRIs** is ***still lower*** than with **TCAs**.

Venlafaxine (Effexor®)#	Desvenlafaxine (Pristiq®)#

Venlafaxine is a ***potent inhibitor*** of **serotonin** reuptake and at ***medium*** to ***higher*** **doses**, is an ***inhibitor*** of **norepinephrine** reuptake (at doses less than 150 mg/day, it has primarily a serotonin effect).

Desvenlafaxine is the active metabolite of **Venlafaxine**.

- **Venlafaxine** is a ***substrate*** but ***not*** an **inhibitor** of CYP2D6.
- **Desvenlafaxine** is a ***minor*** **substrate** for CYP3A4.
- ***Dose***;
  - **Venlafaxine** 75-375 mg/d.
  - **Desvenlafaxine** 50-200 mg/d.
- ***Side effects***; ***similar*** to that of the **SSRIs** (GI effects are common), they are ***can*** cause ***increases*** in blood pressure, which are ***usually*** **mild** and not clinically significant ***unless*** the patient already has **hypertension** that is ***not well*** **controlled**.

Duloxetine (Cymbalta®)# (Cymbatex®)#

Duloxetine is an ***inhibitor*** of **serotonin** and **norepinephrine** reuptake at ***all doses***.
- It is a ***moderate inhibitor*** of CYP2D6.
It is ***indicated for*** the **treatment** of:
1) **Major Depressive Disorder.**
2) **Generalized Anxiety Disorder.**
3) **Diabetic Peripheral Neuropathy.**
4) **Fibromyalgia.**
5) **Chronic Musculoskeletal Pain *caused by* chronic lower back pain** or **osteoarthritis pain.**
- ***Dose***; 40-120 mg/d.
- ***Side effects***; ***similar*** to that of the **SSRI**, ***increase*** **blood pressure**, **tachycardia** (*monitor* blood pressure), **dry mouth** and **constipation**.
- **Duloxetine** can ***cause*** **liver toxicity *and should not*** be **used in patients** with **hepatic insufficiency** and ***severe*** **renal impairment**.

Levomilnacipran (Fetzima®)#

- It is ***primarily metabolized*** by CYP3A4.
It is ***indicated*** for the ***treatment*** of **major depressive disorder** in adults. It is ***not approved*** for the **management of fibromyalgia**.
- ***Dose***; 40-120 mg/day.
- ***Side effects***; ***similar*** to that of the **SSRI**, ***increase*** **blood pressure**, **tachycardia** (*monitor* blood pressure) and **constipation**.

IV) Norepinephrine Reuptake Inhibitors (NRIs)

Reboxetine (Edronax®)#

NRIs *are commonly* used in the treatment of conditions like **ADHD** and **narcolepsy** due to their ***psychostimulant effects*** and in **obesity** due to their ***appetite suppressant effects***. They are also frequently used as ***antidepressants*** for the treatment of **major depressive disorder**, **anxiety** and **panic disorder**.
- **NRIs *may produce*** a **withdrawal syndrome *if*** treatment is ***abruptly*** **stopped**.
- **Reboxetine** is primarily ***metabolized*** by the CYP3A4 isozyme.
Reboxetine is indicated for the ***treatment*** of **depression**.
- ***Most common* side effects** of **Reboxetine**; insomnia, nausea, sweating, dry mouth and constipation.
- ***Contraindications***; **Reboxetine** is ***contraindicated*** in **narrow-angle glaucoma**, **cardiovascular disease**, **epilepsy**, **bipolar disorder**, **patients *concomitantly*** on **MAOIs**.
N.B.; **Atomoxetine** (**Strattera®**) is another norepinephrine reuptake inhibitor ***approved*** for the **treatment** of **attention deficit hyperactivity disorder** (**ADHD**).

V) Atypical Antidepressants

Each drug in this category has a **unique mechanism** of action.

Bupropion (Wellbutrin®)#

Bupropion is a ***weak*** **norepinephrine-dopamine *reuptake* inhibitor** (**NDRI**), the ***exact*** **mechanism** of action remains **unknown**.
It is ***indicated*** for;

- **Major depressive disorder** and **seasonal affective disorder**.
- **Smoking cessation**; it ***reduces*** the **severity** of **nicotine withdrawal symptoms**, but ***somewhat less*** **effective** than **Varenicline** (**Chantix®**).
- **Sexual dysfunction**; it is the ***drug of choice*** for the ***treatment*** of **SSRI-induced sexual dysfunction**.
- **Attention Deficit Hyperactivity Disorder** (**ADHD**); not very common to use it.
- **Obesity**; FDA approves **Bupropion/Naltrexone** (**Contrave®**).

- ***Dose***; **200-450mg/day** (in 2 or 3 divided doses).
- ***Most common* side effects**; ***increased*** **risk of seizures**, **insomnia**, **anxiety**, **irritability**, **headache**, and ***decreased*** **appetite**.

Warning; **Bupropion** ***should not be*** **prescribed** to individuals with **epilepsy** or other conditions that ***lower*** the **seizure threshold**.

- The ***risk*** of **seizures** can be ***minimized*** by the following: **# # # Patient Counselling # # #**

1) ***Avoid*** use in **susceptible patients** (history of seizure disorder and eating disorders).
2) ***Do not*** give ***more than*** **150 mg/dose** or **450 mg/day**.
3) ***Avoid*** **dosage titration** any ***more frequently*** *than* ***every*** **3 days**.

Mirtazapine (Remeron®)#

- **Mirtazapine** ***has*** a ***complex*** **pharmacology** ***mechanisms***.
- ***Not*** cause ***antimuscarinic*** **side effects** like **TCAs**, or interfere with ***sexual function*** like **SSRIs**.

It is ***used primarily*** in the **treatment** of **depression**. It is also ***off-label used*** as an **anxiolytic**, **hypnotic** and **appetite stimulant**.

- **Mirtazapine** may be an ***advantage*** in **depressed patients** ***having*** **difficulty sleeping**.
- ***Dose***; 15-45/day.
- ***Common*** **side effects**; ***Marked*** **sedation**, ***increased*** **appetite**, **weight gain** and **constipation**.
- **Mirtazapine** and **other antidepressants** may ***cause*** a **withdrawal syndrome**.

Trazodone (Trittico®)# | Nefazodone (Serzone®)#

Trazodone ***causes*** ***marked*** **sedation**, **priapism** and **orthostatic hypotension**.

Trazodone in ***low doses*** is commonly ***used*** *off-label* for the **management of insomnia**.

- **Nefazodone** ***unlike*** **Trazodone**, it causes ***minimal effects*** on **sexual function** and is ***less likely*** to cause **orthostatic hypotension**.
- **Nefazodone** has been ***associated*** with a ***risk*** for **hepatotoxicity**.
- ***Dose***; - **Trazodone** 150-300 mg/d. - **Nefazodone** 300-500 mg/d.

Vilazodone (Viibryd®)

- **Vilazodone** is a **serotonin** ***reuptake*** **inhibitor** and a **5-HT$_{1A}$** ***partial*** **agonist**.
- It was approved by the U.S. FDA for ***treatment*** **major depressive disorder** in 2011.
- ***Dose***; ***initial dose***; 10 mg/day with food. ***Maintenance dose***; 20-40 mg/d with food.
- ***Side effect***; similar to the **SSRIs**, including a ***risk*** for **withdrawal syndrome**.

Vortioxetine (Brintellix®)#

- It is ***metabolized*** by CYP2D6. - It is ***used*** for ***treatment*** **major depressive disorder**.
- ***Dose***; ***initial dose***; 10 mg/day. ***Maximum dose***; 20mg/d.
- ***Most common*** **side effects**; **Nausea**, **vomiting** and **constipation**.

VI) Monoamine Oxidase Inhibitors (MAOIs)

Non-selective (MAO-A & MAO-B) Inhibitors (*Irreversible*)

Phenelzine (Nardil®) | **Isocarboxazid** (Marplan®) | **Tranylcypromine** (Parnate®)

Selective MAO-A Inhibitors (*Reversible*)

Moclobemide (Aurorix®)

- The use of **MAOIs** ***with*** **other antidepressants** is ***contraindicated***.

Drug Switching; - ***From*** **another antidepressant** ***to*** an **MAOI**; Wait for 2 weeks after the antidepressant is discontinued before initiating the MAOI (***except*** for **Fluoxetine**, waiting for 5-6 weeks).
- ***From*** an **MAOI** ***to*** **another antidepressant**; Wait for 2 weeks.

- ***Side effects***; ***Severe*** and ***unpredictable***, due to **drug-food** and **drug-drug interactions**. ***Most common***; **drowsiness**, **hypotension**, **blurred vision**, **dry mouth** & **constipation**.

 # # # Drug-Food Interaction (Cheese Reaction) # # #

- **Tyramine**, ***found*** in **foods**, such as **aged** (or **rip**) **cheeses**, **meats**, **chicken liver**, **pickled** or **smoked fish** and **red wines**.
- **Tyramine** acts as **catecholamine** ***releasing agent*** & **normally** ***inactivated*** by **MAO** in the **gut**.
- **Patients** ***taking*** **MAOI** are ***unable*** to **degrade tyramine** obtained from the diet ⇨ ***release*** of **large amounts of catecholamines** from nerve terminals ⇨ **hypertensive crisis** (headache, stiff neck, tachycardia, nausea, hypertension, cardiac arrhythmias, seizures and stroke).

Lithium Therapy

Lithium (Li^+) Carbonate (Prianil®)#

Lithium was the ***first*** mood-stabilizing medication ***approved*** by the FDA in the 1970s for treatment of **mood disorders**.

- **Lithium** has been used for the ***treatment*** of **mania** for ***over*** **60 years**, yet the ***exact*** **mechanisms** remain ***unclear***.
- **Lithium salts** are ***used acutely*** and ***prophylactically*** for **managing bipolar patients**.
- **Lithium** is ***effective*** in **treating 60-80%** of **patients *exhibiting*** **mania** and **hypomania**.

Pharmacokinetics;

Absorption	- Complete absorption within 6-8 hours. - Peak plasma levels in 30 minutes to 2 hours.
Therapeutic index	- The therapeutic index of lithium is extremely low.
Distribution	- Initial volume of distribution is 0.5 L/kg, rising to 0.7-0.9 L/kg. - No protein binding.
Metabolism	- Non
Excretion	- More than 95% urinary and any renal impairment delays it. - Half-life is 20–24 hours.
Plasma conc.	- 0.6-1.4 mEq/L.
Dose	- 0.5 mEq/kg/d in divided doses (600-900 mg/day).

- ***Dose***;
  1) **Pre-lithium workup**; patient confirm the following; a complete blood cell count, electrolytes, renal function, thyroid function tests, urinalysis, electrocardiogram (ECG) and pregnancy test for women.
  2) **Dosing**; ***Initial***; **600-900 mg/day** in ***divided doses*** and then ***titrated*** *according to* **response** and **tolerability**.
  3) **Monitoring**; **Li^+ serum concentrations *must be* monitored**.
     - ***Serum concentrations***; **0.8-1.2 mEq/L** in ***acute mania*** & **0.6-1.0 mEq/L** in ***maintenance***.
     - These measurements are taken **10-12 hours *after*** the **last dose**.
     - ***Initial determination*** serum concentrations ***should be*** obtained about **5 days *after*** the **start of treatment** (at which time steady-state conditions should have been attained).
     - ***After dose changing***; serum concentration obtained 3 days after dosage changes.
     - ***Perform*** **renal function tests**, **thyroid function tests**, and a **urinalysis *every*** **6-12 months**.

Side effects;

  * ***Neuromuscular***; **Tremor** is one of the most common side effects. **Lithium-induced tremor** can be ***treated*** with **Propranolol** (or **Atenolol**) or **reduce dose**.
  * ***CNS***; **Confusion** and **Agitation**; ***treated*** by **reduce dose**.
  - ***GIT***; **Nausea**, **Vomiting** and **Diarrhea**; ***treated*** by **reduce dose** or **extended-release**.
  * **Hypothyroidism**; ***treated*** by ***discontinue*** **Li^+** or ***give*** **levothyroxine**.
  * ***Kidney***; **Polydipsia** and **Polyuria**; ***due to*** loss of responsiveness to antidiuretic hormone (nephrogenic diabetes insipidus). ***Treated by***; **reduce dose** or use of **Amiloride** or *single bedtime low dose of* **Thiazide** or **NSAIDs** (block Li^+ uptake by kidney tubules). **Nephrotoxicity** may occur during ***long-term*** **lithium therapy**.
  - ***Pregnancy***; **Teratogenicity**; ***Avoid*** during **first trimester**, if possible.
  * ***Others***;
    - ***CVS***: **Arrhythmia** and **Hypotension** may occur.
    - ***Dermatologic***: **Rash**, **Alopecia** and exacerbation of **Psoriasis**.
    - **Edema** and **Weight gain**.

- ***Drug Interactions***; **Thiazides**, **NSAIDs**, **Aminophylline**, **Theophylline** and **ACEIs**.

Stimulants (Psychostimulants)

Stimulants (Psychostimulants)

Stimulants are the ***first-line therapy*** and probably the ***most effective*** **treatment** ***for*** **Attention Deficit Hyperactivity Disorder (ADHD)**
Stimulants are ***preferred*** to **other medications** ***because*** stimulants have a **rapid onset of action** and **long record of safety** and **efficacy**.
All stimulants have ***similar efficacy but differ*** by **dosing, duration of action**, and **adverse effect** profiles in individual patients.
Stimulants may cause ***significant*** **insomnia** ***if taken*** at **night**.
Most common **adverse effects** of stimulants include **appetite suppression** and **weight loss, headaches** and **mood effects** (depression, irritability).
Stimulant medications do ***enhance*** **mental executive** ***functions*** for those with **ADHD**.
Most commonly **stimulants** ***for*** **ADHD** are **phenethylamines**: **Amphetamine** (**Adderall**®), **Methylphenidate** (**Ritalin**®), **Dexmethylphenidate** (**Focalin**®), **Dextroamphetamine** (**Dexedrine**®), **Dextromethamphetamine** (**Desoxyn**®) & **Lisdexamfetamine** (**Vyvanse**®).

Amphetamine (Adderall®)#

Amphetamine is a ***potent CNS stimulant***, marked ***stimulant effects*** on mood and alertness and a ***depressant effect*** on appetite. It is has a **mood-elevating (*euphoria*) effect**.
Uses; - **Attention Deficit Hyperactivity Disorder (ADHD)**
- **Narcolepsy** (*chronic sleep disorder*).
Off-label: **Performance-enhancing, Improve work performance, Depression** and **Obesity**.
Side effects; ☞ ***Cardiovascular***; Palpitations and increase blood pressure.
☞ ***CNS***; Insomnia, anxiety, confusion, hallucination and tremor.
☞ ***Other***; Weight loss, painful urination, headache, nausea, vomiting, abdominal cramps and diarrhea or constipation.
FDA Warning; **# # # # AMPHETAMINES-RELATED DEATH # # # #**
- *Administration of* **amphetamines** for ***prolonged periods*** of time may lead to ***drug dependence***, and, therefore, this must be avoided.
- ***Misuse*** of **amphetamines** may cause ***sudden*** **death** and ***serious*** **cardiovascular events** (**heart attack** and **heart stroke**).

Dextroamphetamine (Dexedrine®) | Lisdexamfetamine (Vyvanse®)

Dextroamphetamine is the ***more active*** *enantiomer* of the **Amphetamine** molecule.
Lisdexamfetamine is a ***prodrug*** that is converted to active component **Dextroamphetamine**.

Methamphetamine (Desoxyn®)

Methamphetamine also known as "***speed***".
- It is like amphetamine ***but***; much stronger, act quicker, and can be considered more addicting.
Uses: ***approved by the FDA for treating*** ☞
- **Attention Deficit Hyperactivity Disorder (ADHD)**.
- **Exogenous obesity**: obesity originating from factors outside the patient's control.
Off-Label: **Increase sexual desire, lift the mood, increase energy, depression** & **narcolepsy**.

Methylphenidate (Ritalin®)#

- **Methylphenidate** is an amphetamine derivatives with ***less*** **side effects**.
- **Addiction** and **psychological dependence** are ***rare*** with methylphenidate.
It is presently one of the ***most prescribed*** medications in **ADHD**.
It is also effective in the treatment of **narcolepsy**.
Off-label: **Depression** and **performance-enhancing**.

Modafinil (Provigil®)# (Bravamax®)# | Armodafinil (Nuvigil®)# (Armowake®)#

Modafinil is a ***wakefulness-promoting agent*** (**Armodafinil** is the ***enantiopure*** of **Modafinil**)
Uses: **sleep disorders**; **narcolepsy**, **obstructive sleep apnea** (**OSA**) and **shift work disorder** (**SWD**). In the US military, it has been used on certain Air Force missions as a "**go pill**".
- ***Dose***; 200 mg **Modafinil** (150 mg **Armodafinil**) once a day in morning or 1 hr before start of work shift.

Fenethylline (Captagon®)#

Fenethylline is a ***prodrug***, it is metabolized to form two drugs **amphetamine** and **theophylline**.
Most of the **amphetamines** abused in **Saudi Arabia** and ***other*** **Arab countries** come in the form of **Captagon tablets**.

Non-Stimulants

Atomoxetine (Strattera®)#

Atomoxetine is a **norepinephrine reuptake inhibitor** approved for the ***treatment*** of **attention deficit hyperactivity disorder** (**ADHD**).
It has become a ***second-line*** and, in ***some cases***, ***first-line*** treatment in **children** and **adults** ***with*** **ADHD** ***because*** of its **efficacy**.
- The ***initial*** **therapeutic effects** usually take **2-4 weeks** to ***become*** **apparent**.
- It can be ***abruptly*** **stopped** ***without significant*** **withdrawal effects**.
- ***Dose***; ranges from 40mg/day to 100mg/day given in 1-2 divided doses
- ***Side effects***; Insomnia, dry mouth, cough, decreased appetite, upset stomach, nausea or vomiting, dizziness, drowsiness, problems urinating, irritability, constipation, skin rash, itching, increased menstrual cramps, increase blood pressure and sexual side effects including impotence, loss libido or trouble having an orgasm.
- ***Drug interactions***; **CYP2D6 inhibitors** ***such as*** **Bupropion** or **Fluoxetine** ⇨ ↑ plasma atomoxetine levels (**Atomoxetine** is a substrate for **CYP2D6**) and **MAOIs**.

Clonidine (Kapvay®)#

Clonidine is a ***centrally acting*** **α_2-adrenergic agonist** used as **antihypertensive agent**.
In **2010 US FDA** has ***approved*** **Kapvay®** (**Clonidine Hydrochloride**) ***extended-release*** for the ***treatment*** of **ADHD** as ***monotherapy*** and as ***adjunctive therapy*** to **stimulant medications**, for paediatric patients aged 6-17 years. It was later approved for adults.
- ***Dose***; should be ***initiated with*** **one 0.1 mg** tablet at **bedtime**, ***if*** **dose** ***equal*** or ***higher than*** **0.2 mg/day**, **doses** should be taken **twice** a day (max. dose; 0.4mg/day).
- ***Most common side effects*** and ***precautions***;
  - **Hypotension** and **bradycardia**; dose-related decreases in blood pressure and heart rate.
  - **Sedation** and **somnolence**.
  - **Rebound hypertension**; in ***abrupt discontinuation***.
- **Warning**; ***Sudden*** **deaths** have been ***reported*** in **children** taking **Clonidine** with **Methylphenidate** at **bedtime**.

Guanfacine (Intuniv®)#

Guanfacine ***like*** **Clonidine**, is a ***centrally acting*** **α_2-adrenergic agonist**, used in the ***treatment*** of **ADHD** and **hypertension**.
Like **Clonidine**, in **2010 US FDA** has ***approved*** **Intuniv®** (**Guanfacine Hydrochloride**) ***extended-release*** for the ***treatment*** of **ADHD** as ***monotherapy*** and as ***adjunctive therapy*** to **stimulant medications**, for paediatric patients aged **6-17 years**.
- ***Dose***; should be ***initiated with*** 1 mg/day once and adjust in increments of no more than 1 mg/week. Target dose range (0.05 - 0.12 mg/kg/day). ***Dosage adjustments*** are recommended with concomitant use of ***strong*** **CYP3A4 inhibitors**.
- ***Most common side effects*** and ***precautions***; same as **Clonidine**.

Antipsychotic Drugs

The **antipsychotic drugs** (***also called*** **neuroleptics** or **major tranquilizers**) are **used** ***primarily*** to treat **schizophrenia**, but they are ***also effective*** in **other psychotic** and **manic states**.

- **Antipsychotic drugs** are ***not*** **curative** and ***do not eliminate*** **chronic thought disorders**, but they often ***decrease*** the **intensity of hallucinations** and **delusions**.

The **antipsychotic drugs** are ***divided into*** **first generation** and **second generation** agents.

First-generation antipsychotics, ***known as*** **typical antipsychotics**, while **second-generation antipsychotics**, ***known as*** **atypical antipsychotics**.

The **first-generation** drugs are ***further classified as*** "**low potency**" or "**high potency**".

- ***This*** **classification** ***does not indicate*** **clinical effectiveness** of the drugs, ***but*** rather specifies ***affinity*** for the **dopamine D_2 receptor**, which, in turn, may ***influence*** the **adverse effect** of drug.

First-Generation Antipsychotics; FGAs (Typical)

Low Potency

Fewer **extrapyramidal symptoms**; (**EPS**), *but* ***more*** **H_1**, **α_1** and **muscarinic** ***blocking effects***.

Phenothiazines	
Chlorpromazine (CPZ) (Neurazine®)#	**Thioridazine** (Mellaril®)

High Potency

More **extrapyramidal symptoms** (**EPS**), *but* ***less*** **H_1**, **α_1** and **muscarinic** ***blocking effects***.

Phenothiazines	
Fluphenazine (Modecate®)#	**Perphenazine** (Trilafon®)
Mesoridazine (Serentil®)	**Trifluoperazine** (Stelazine®)
Prochlorperazine (Compazine®)#	**Promethazine** (Phenergan®)#
Butyrophenones	
Haloperidol (Haldol®)#	**Droperidol** (Inapsine®)
Others	
Loxapine (loxitane®)	**Zuclopenthixol** (Clopixol®)#
Pimozide (Orap®)	**Thiothixene** (Navane®)

Second-Generation Antipsychotics; SGAs (Atypical)

Lower incidence of **EPS** and have ***little*** or ***no*** have effect on **H_1**, **α_1** and **muscarinic** receptor than the **first-generation** agents, they are ***associated with*** a ***higher risk*** of **metabolic side effects**, such as **diabetes**, **hypercholesterolemia** and **weight gain**.

Second-generation agents are ***generally*** used as ***first-line therapy*** for **schizophrenia** to ***minimize*** the ***risk of*** EPS ***associated*** with the **first-generation agents**.

The **second-generation drugs** appear to owe their unique activity to ***blockade*** of ***both*** **serotonin** and **dopamine** and **other receptors**.

Clozapine (Clozaril®)#	**Aripiprazole** (Abilify®)#	**Olanzapine** (Zyprexa®)#
Paliperidone (Invega®)#	**Quetiapine** (Seroquel®)#	**Risperidone** (Risperdal®)#
Lurasidone (Latuda®)#	**Iloperidone** (Fanapt®)#	**Ziprasidone** (Zeldox®)#
Asenapine (Saphris®)#	**Sertindole** (Serdolect®)#	**Sulpiride** (Dogmatil®)#

Only **Ziprasidone** and **Paliperidone**; ***increased*** **absorption** ***with*** **food**.
Haloperidol can be ***given*** **IM** (**IV** has been linked to toxicity and ***should not be given***).
All of **first-generation** and ***most*** of the **second-generation** ***block*** **D_2 dopamine receptors**.
Most of **second-generation** **agents** ***inhibit*** **5-HT receptors**, ***particularly*** **5-HT_{2A}** receptors
Long acting parenteral (**IM**) **formulations** (***only for*** **chronic therapy** in patients who have ***trouble*** **adhering** to **oral therapy**);
- **Depot forms** (***long-acting forms***) of **Haloperidol**, **Fluphenazine**, **Zuclopenthixol** and **Risperidone** are ***available***, providing ***sustained*** **concentrations** for about **1 month** ***for*** **Haloperidol** and **2-3 weeks** for **Fluphenazine**, **Zuclopenthixol** and **Risperidone** (***only for chronic therapy***).
- **Paliperidone Palmitate** (**Invega® Sustenna**) (*FDA approved 5/2015*); It is a **3-month** ***extended-release*** **injectable suspension**.
- **Olanzapine Palmitate**; ***once monthly***, it is also available.
- **Aripiprazole Monohydrate** (**Abilify® Maintena**); ***once monthly***, also available.

- **Asenapine** (**Saphris®**); is ***available*** in a **sublingual formulation**; 5-10 mg twice daily.

Uses;

A) Psychiatric Indications;
- **Schizophrenia**; is the ***primary*** **indication** for **antipsychotic agents**.
- **Psychotic bipolar disorder** (**BP-I**), **psychotic depression** and **treatment-resistant depression**; **Chlorpromazine**, **Aripiprazole**, **Olanzapine**, **Quetiapine**, **Risperidone** & **Ziprasidone** are ***approved*** by the FDA for **treatment** of the **manic phase** of **bipolar disorder**.
- **Schizoaffective disorders**; characteristics of both **schizophrenia** and **affective disorders** (**depression**, **bipolar disorder** & **anxiety disorder**).
- **Tourette's syndrome** and ***disturbed behavior*** in patients with **Alzheimer's disease**.

B) Non-psychiatric Indications;
- **Prevention of nausea and vomiting**; ***most*** of ***older*** **typical antipsychotic drugs** (***except*** **Thioridazine**) have a ***strong*** **antiemetic effect**, **Prochlorperazine** used as antiemetic.
- **Neuroleptanalgesia in medical procedure**; **Droperidol** (typical antipsychotic) is **used** in ***combination*** with **Fentanyl** (opioid) in **neuroleptanalgesia**.

- ***Doses***;

Most Common	Minim Effective Dose (mg)	Usual Daily Doses (mg)
Chlorpromazine	100	100-1000
Fluphenazine	2	2-60
Haloperidol	2	2-60
Clozapine	50	300-600
Aripiprazole	10	10-30
Olanzapine	5	10-30
Quetiapine	150	150-800
Risperidone	4	4-16
Ziprasidone	40	80-160

Side effects;

A) *Serious Side Effects*;

1) **Extrapyramidal Side Effects (EPSE)**; ***drug-induced*** **movement disorders**; **Dystonia**, **Akathisia**, **Pseudoparkinsonism** and **Tardive Dyskinesia** (**Clozapine** has ***not been associated*** with **tardive dyskinesia**).
2) **Neuroleptic Malignant Syndrome (NMS)**; **agitation**, **confusion**, **consciousness disturbance**, **fever**, **tachycardia**, ***unstable*** **blood pressure** and **sweating**.

B) *General Side Effects*;

1) **Sedation and drowsiness**; ***Due to*** **antihistaminic effects**, ***usually*** during the **first few weeks** of treatment, ***particularly*** with **Chlorpromazine**, **Olanzapine**, **Quetiapine** & **Clozapine**.
2) **Antimuscarinic**; ***Particularly***; **Thioridazine**, **Chlorpromazine**, **Clozapine** and **Olanzapine** may produce blurred vision, dry mouth (except **Clozapine**), urinary retention and constipation.
3) **Orthostatic Hypotension and light-headedness**; ***Due to*** **block α_1 receptors**.
4) **Hyperprolactinemia**;
   - ***In female***; Menstrual disturbance (**amenorrhea**) & **galactorrhea**.
   - ***In male***; **Gynecomastia** and **impotence** (erectile dysfunction).
5) **Sexual Dysfunction**:
   - ***Erectile problems*** occur in 23-54% of men.
   - ***Loss*** of **libido** may occur in **men** and **women**.
6) **Weight Gain**;
   - This occurs in up to 40% of patients, with ***low-potency agents*** having ***higher*** **risk**.
   - Weight gain may occur because of ***actions*** at **histamine** or **serotonin receptors**.
7) **Risk of Venous thromboembolism (VTE)**.

C) *Specific Side Effects for Typical Antipsychotics*;

- ***Low-potency agents*** (**Thioridazine** and **Chlorpromazine**) can cause **pigmentary** ***deposits*** on the **retina** and **corneal opacity**.
- ***Many*** of the **typical agents** (**Thioridazine**, **Pimozide**, and ***IV*** **Haloperidol**) can cause ***serious*** **ECG changes** (e.g., **QT interval** ***prolongation***), these changes can ***lead to*** **arrhythmias** and **death**.

D) **Clozapine *Serious Side Effects***:

1) **Agranulocytosis**; ***risk*** of **serious** or **fatal infections**.
   - It is occurs ***about*** **1-2%** and is ***highest*** during the ***first*** **4-6 months of therapy**.
   - It is ***contraindicated*** if the white blood cell count is ***less than*** 3500 cells/mm^3.
   - Patients ***must be*** **enrolled** in a **Clozaril registry program**, which ***monitors*** **neutrophil** and **white blood cell** ***counts***.
2) ***Black box warnings***; **seizures** (at higher doses) and **myocarditis**, **orthostatic hypotension** and **respiratory arrest**.

FDA Warning;

- ***Most*** **of antipsychotics** *may* ***lower*** the **seizure threshold** and ***should be*** **used** ***cautiously*** in **patients** with **seizure disorders** or **those** with an ***increased*** **risk for seizures**, such as **withdrawal from alcohol**.
- ***Most*** **of antipsychotics** also carry the **black box warning** of ***increased risk*** for **mortality** when used in **elderly patients *with* dementia related psychosis**.

Drugs for Neurodegenerative Diseases

Antiparkinsonian Drugs

I) Levodopa (L-dopa)

Levodopa/Carbidopa (Sinemet®)# (Parcopa®)

Dopamine *can't* be given in the treatment of PD as it *doesn't* penetrate the BBB.
Dopa is the amino acid *precursor* of Dopamine.
Levodopa (L-dopa) is the *levorotatory stereoisomer* of dopa.
Levodopa is *metabolized* to Dopamine by the *dopa-decarboxylase* enzyme.
> 95% of Levodopa is *metabolized* outside the brain by peripheral *dopa-decarboxylase*.
Only about 1-3% of Levodopa *enters* the brain.
Levodopa is *combined* with peripheral *dopa-decarboxylase* inhibitors (DDCI); Carbidopa and Benserazide (doesn't cross BBB) ⇨ *Prevents some* of the peripheral conversion of Levodopa to Dopamine ⇨ *increase* brain level of Levodopa.
Dose; - 75 mg/day of Carbidopa is *usually inhibit* peripheral decarboxylase activity.
- *Formulation* of Carbidopa/Levodopa (Sinemet®; 25/100, 50/200); available as orally disintegrating tablet, that *disintegrates* in the mouth and is swallowed *with the* saliva.
- It *should be* taken 30-60 minutes *before* meals.

Formulations;
1) Standard Formulation (SF): initial dose, 25 mg/100 mg 1 tablet orally three times daily, and *gradually increased* (dose titration)..
2) Controlled-release (CR) Formulation: 1 tablet orally two or three times daily.
- N.B.; If patient need conversion from SF to CR, see guidelines for conversion.
3) Combination (Stalevo®); Levodopa, Carbidopa and Entacapone.

Side effects;
A) Acute Side Effects (Levodopa/Carbidopa);
1) GIT Effects; Nausea and vomiting; < 20% and can tolerate in higher doses.
2) CVS Effects; Orthostatic hypotension and cardiac arrhythmias; < 10%.
3) CNS Effects; Depression, insomnia, agitation & hallucinations; < 10%.
B) Long-term Side Effects (Levodopa/Carbidopa)*;
1) Response Fluctuations;
a) Wearing-off phenomenon or end-of-dose akinesia (timing of doses);
- *Characterized by*; *Return* of Parkinson symptoms *before* the next dose.
- *Treatments*; *adding* a dopamine agonist or MAO-B inhibitor, or COMT inhibitor or *increasing* the frequency/dose of levodopa.
b) On-off phenomenon (*unrelated* to the timing of doses);
- *Characterized by*;
- Off; Off-periods of *marked* akinesia.
- On; On-periods of *improved* mobility.
- *Treatments*; *adding* Entacapone, Rasagiline, Pramipexole, Ropinirole, Apomorphine & Selegiline or *redistributing* dietary protein.
2) Dyskinesia;
- Is a *drug-induced* involuntary movements including chorea & dystonia.
- Treatments; *decrease* Levodopa dose or *adding* Amantadine (*antidyskinetic*).

N.B; A drug holiday (discontinuance of the drug for 3-21 days) may temporarily improve responsiveness to levodopa but is usually little help.

- *Drug interactions*;
A) If Levodopa used alone; Pyridoxine (Vitamin B_6) and MAO-A inhibitors.
B) Levodopa/Carbidopa; Antihypertensive agents, TCAs, D_2 antagonists and Iron.
- *Contraindications*; - Closed-angle glaucoma.
- Cardiac arrhythmia & peptic ulcer patients must be managed carefully.
- Suspicious, undiagnosed skin lesions or a history of melanoma patients.

II) Dopamine Receptor Agonists

Ergot Derivatives

Bromocriptine (Parlodel®)#

Bromocriptine is an ***ergot*** (***ergoline***) ***derivative***, is a **dopamine agonist** that is used in the ***treatment*** of **Parkinson's disease**, **Hyperprolactinaemia** and **Neuroleptic Malignant Syndrome** (**NMS**).
- The ***older*** **ergot derivatives** (**Bromocriptine** and **Pergolide**) have been ***widely*** used to treat **Parkinson's disease** ***in the*** **past** ***but*** are **now** ***rarely*** **used**.
- ***Dose*** for **parkinsonism**; **5-40 mg/day**.
- ***Side Effects***; **Hallucinations**, **confusion**, **delirium**, **nausea** & **orthostatic hypotension**.
  - ***Potential*** to cause **pulmonary** and **retroperitoneal fibrosis**.
- ***Used with caution*** in patients with history of **myocardial infarction** or **peripheral vascular disease**.

Non-ergot Derivatives

Apomorphine (Apokyn®)#	**Pramipexole** (Mirapex®)#
Ropinirole (Requip®)#	**Rotigotine** (Neupro®)#

- They are ***non-ergot*** **dopamine agonists**; ***approved for*** the ***treatment*** of **Parkinson's**.

Pharmacokinetics;
  - **Pramipexole** & **Ropinirole** are ***available*** **orally** in ***extended-release*** formulations.
  - **Apomorphine** is ***available*** **injectable** formulation.
  - **Rotigotine** is ***available in*** **transdermal** formulation (***once-daily***).

Indications; - **Apomorphine** is ***used for*** **acute management** of the **hypomobility** "**off**" **phenomenon** in ***advanced*** **Parkinson's disease**.
  - **Pramipexole**, **Ropinirole** and **Rotigotine** used for **Parkinson's disease** and **Restless Legs Syndrome** (**RLS**).

Side Effects; **Hallucinations**, **confusion**, **delirium**, **nausea** & **orthostatic hypotension**
  - ***Unlike*** the **ergot derivatives**, these agents do ***not exacerbate*** **peripheral vascular disorders** or **cause fibrosis**.

Notes; - **Apomorphine** ***drug interaction***; **5-HT3 antagonist antiemetics** (e.g., **Ondansetron**, **Dolasetron**, **Granisetron**); risk of severe hypotension.
  - **Apomorphine** ***contraindications***; sulfite sensitivity/allergy patients.

III) Monoamine Oxidase-B (MAO-B) Inhibitors

Selegiline (Eldepryl®)	**Rasagiline** (Azilect®)

Formulations; - **Selegiline**; **tablets**, **orally dissolving tablets** and **patches**. The patches (**Emsam**®) are FDA approved ***only for*** **depression**.
  - **Rasagiline**; ***once daily*** **tablets**.

Dose; - **Selegiline**; - **Tablets**; 5 mg orally twice daily (morning and noon).
  - **Disintegrating tablets**; 1.25-2.5 mg/day.
  - **Rasagiline**; 0.5-1 mg/day orally.

- **Selegiline** is ***metabolized to*** **amphetamine-like substances**, may produce insomnia if the drug is administered at night, (**Rasagiline** is not metabolized to an amphetamine-like substance).
- **Selegiline** may **administered** ***with*** **Levodopa**, it ***enhances*** the **actions** of **Levodopa** and substantially ***reduces*** the **required dose**.
- ***Common Side Effects***; **Nausea**, **hallucinations** and **orthostatic hypotension** (**insomnia** ***only with*** **Selegiline**).
- ***Drug Interactions***;
  - **Selegiline**; ***with*** **Meperidine** ⇨ ***increase risk*** of **serotonin syndrome**.
  - **Rasagiline**; ***with*** **Tramadol**, **Methadone**, **Dextromethorphan**, **Sympathomimetics**, **Fluoxetine**, or **Fluvoxamine** ⇨ ***increase risk*** of **serotonin syndrome**.
  - **Ciprofloxacin** ↑ **Rasagiline** **concentration** (through **CYP1A2** ***inhibition***).

IV) Catechol-O-Methyltransferase (COMT) Inhibitors

Tolcapone (Tasmar®)	**Entacapone** (Comtan®)

- **Tolcapone** has both **central** & **peripheral** ***effects***, whereas the effect of **Entacapone** is **peripheral**.

Tolcapone is ***severely*** **widely restricted** ***because*** of **hepatotoxicity** (**Entacapone** has ***largely replaced*** **Tolcapone**).

COMT inhibitors ***reduce*** the **symptoms** of **fluctuations response** in ***patients*** used **Levodopa/Carbidopa**.

- ***Side effects***; **Dyskinesia**, **nausea**, **diarrhea**, **urine discoloration** (**orange**) and **hallucinations**.

Stalevo®; ***Consists of*** a ***combination*** of **Levodopa/Carbidopa/Entacapone**. It is available in ***three*** **strengths**:

Stalevo® 50 (50/12.5/200 mg)
Stalevo® 100 (100/25/200 mg)
Stalevo® 150 (150/37.5/200 mg)

V) Other Agents

Anticholinergic Agents

Benztropine (Cogentin®)#	**Trihexyphenidyl** (Parkinol®)	**Biperiden** (Akineton®)#
Procyclidine (Kemadrin®)	**Orphenadrine** (Norflex®)#	

- **Anticholinergic drugs** were the ***first*** **pharmacological agents** used in the ***treatment*** of **Parkinson's disease** (**Orphenadrine** is the first agents used in 1940s).
- **These agents** may ***improve*** **tremor** & **rigidity** ***but*** have ***little effect*** on **bradykinesia**.
- ***Dose***;
  - **Trihexyphenidyl**; ***initial dose*** 0.5 mg orally twice daily, ***maintenance*** 6- 10 mg/day.
  - **Benztropine**; ***initial dose*** 0.5 mg orally twice daily, ***maintenance*** 1-6 mg/day.
  - **Biperiden**; **2 mg** orally 3 to 4 times a day.
  - **Orphenadrine** is a ***derivative*** of the ***first-generation*** **antihistamine** **Diphenhydramine** and has effects to ***block*** **muscarinic receptors**, ***now rarely*** **used** **in Parkinson's disease** (it is particularly toxic in overdose), ***but*** **used** in ***acute*** **painful musculoskeletal conditions**.
- ***Common Side Effects***; **Confusion**, **dry mouth**, **dry eyes**, **urinary retention** and **constipation**.

Other Agent

Amantadine (Symmetrel®)# (PK-Merz®)#

Amantadine is an **antiviral agent**, was ***by chance*** found to have ***Antiparkinsonism properties***.

It has ***symptomatic*** **benefits** and may ***reduce*** **dyskinesia** caused by **Levodopa** or **dopamine agonists**.

- ***Dose***; 100 mg orally 2-3 times daily (***caution*** in **renal dysfunction**).
- ***Side effects***; **Dizziness**, **insomnia**, **livedo reticularis**, **nausea** and **nightmares**.

Drugs for Alzheimer's Disease

I) Cholinesterase Inhibitors

Tacrine	Donepezil (Aricept®)#
Rivastigmine (Exelon®)#	Galantamine (Reminyl®)#

- The *inhibition* of **acetylcholinesterase (AChE)** *within* the **CNS** will *improve* **cholinergic transmission**, at least at those neurons that are still functioning.

Tacrine was the *first* to *become* **available**, it has been *replaced* because of its **hepatotoxicity**.

Donepezil, **Galantamine** and **Rivastigmine** are *reversible* **AChE inhibitors** *approved for* the **treatment of mild to moderate Alzheimer's disease**.

- **All of them** have *some* **selectivity** for **AChE** in the **CNS**, as *compared to* the **periphery**.

***Only* Donepezil** is *approved for* **treatment of advanced Alzheimer's disease**.

Rivastigmine is the *only* **AChE inhibitor** *available* as a **transdermal** *formulation* and the **only agent** *approved for* the **management of dementia associated with Parkinson's disease**.

- **All of them** *except* **Rivastigmine** are substrates for **CYP450**; *potential* **drug interactions**.

- ***Doses***; - **Donepezil**; - For ***mild* to *moderate* AD**; 5-10 mg once daily.
  - For ***moderate* to *severe* AD**; 10 or 23 mg once daily.
  - **Rivastigmine**; - **Tab.**; 1.5 mg orally twice daily, with a maximum dose of 12 mg/day.
  - **Transdermal patches**;
  - **Initial**; **4.6 mg/24 hours**, dose increased slowly (minimum 4 weeks) to **9.5 mg/24 hours** (*maximum effective* dose of **13.3 mg/24 hours**).
  - * **Transdermal patch 13.3 mg/24 h** is *approved* for **all stages** of AD, *including severe*.
  - **Galantamine**; - **Immediate-release** *formulation*; 4 mg twice daily (initial).
  - **Extended-release** *formulation*; 8 mg once daily (initial).
  - *Maintenance dose* after dose titration is 16-24 mg/day.

- ***Side effects***; **nausea, diarrhea, vomiting, anorexia, tremors, bradycardia & muscle cramps**.

II) N-Methyl-D-Aspartate Antagonists

Memantine (Ebixa®)#

- *Overstimulation* of **glutamate receptors**, *particularly* of the **NMDA type**, may *result* in **excitotoxic effects** on **neurons** and is *suggested as* a **mechanism** *for* **neurodegenerative** or **apoptotic** (programmed cell death) **processes** via **Ca^{2+}** *release* **mechanism**.

Memantine is an **NMDA receptor** *antagonist* *first used* as an **anti-influenza** *agent*, it indicated for **moderate to severe Alzheimer's disease** and in **dementia with Lewy bodies**.

- It acts by ***blocking*** the **NMDA receptor** and *limiting* **Ca^{2+} influx** into the **neuron**.

- ***Dose***; - ***Immediate-release***; 5 mg once daily, can titrated to a maximum dose of 20 mg/day.
  - ***Extended-release***; 7 mg once daily, can titrated to a maximum dose of 28 mg/day.

- ***Common side effects***; **Confusion, dizziness, drowsiness, headache, insomnia** and **agitation**.

Nutritional Supplement

Caprylidene (Axona®)#

- **Axona** is a **medical food** used as a dietary management of the impairment of metabolic processes associated with **mild to moderate Alzheimer's disease**.
- **Axona** has *not* been **approved** by the **US FDA** for **Alzheimer's disease**.

Drugs for Multiple Sclerosis

I) Disease-Modifying Therapies (DMTs)

Beta Interferons

Interferon β-1a (Avonex®)# (Rebif®)# | **Interferon β-1b** (Betaseron®)# (Extavia®)#

Peginterferon β-1a (Plegridy®)#

The ***first medication*** *approved by* the **FDA** for **MS**, in **1993**, was **Interferon beta-1b**.
Peginterferon β-1a; is an **Interferon beta-1a** ***conjugated to*** a **polyethylene glycol** to ***decrease*** **frequency of injections** (every 2 weeks), it is ***approved by*** in **2014** for **MS**.
Most common side effects; **Skin reactions** (at the injection site, more common in SC injection), **flulike symptoms** (fever, muscle aches, fatigue and headaches, usually disappear after 3 months and can be treated with NSAIDs such as **Ibuprofen**), **leukopenia** (*reduce* white blood cells count) and ***affect*** **liver function**.
Neutralizing antibodies (**NAbs**); The ***development of*** **neutralizing antibodies** is a ***major problem*** in **multiple sclerosis patients** ***treated with*** **Interferon-beta** that can ***reduce*** **drug effectiveness**.

Non-Beta Interferons

Glatiramer Acetate (Copaxone®)#

Approved for the ***reduction*** of the **frequency of relapses** in ***patients with*** **MS**.
- ***Most common side effects***; **Skin reactions** (at the injection site), **flulike symptoms**, **flushing**, **chest tightness**, **palpitations**, **anxiety** and **shortness of breath**.

Dimethyl Fumarate (DMF) (Tecfidera®)#

- **Dimethyl Fumarate** is the methyl ester of fumaric acid.
- It have **immunomodulatory properties** ***without significant*** **immunosuppression** to ***reduce*** **relapse rate** and ***increased*** **time** to **progression** of **disability** in **MS**.
- ***Dose***; 120 mg orally twice daily, then increased to the maintenance dose of 240 mg twice daily.
- ***Most common side effects***; **Skin flushing**, **GIT effects** (abdominal pain, diarrhea and nausea) and **lymphocytopenia** (risk of infections).

Fingolimod (Gilenya®)#

It is the ***first oral disease-modifying drug*** ***approved by*** the **FDA** in **2010** to ***reduce*** **relapses** & ***delay*** **disability progression** in ***patients with*** **relapsing forms** of **MS**.
It is ***derived from*** **Myriocin**, a metabolite of the fungus *Isaria sinclairii*, the **treatment cost** is ***very expensive*** (**GILENYA®** 0.5mg 28 cap.; 15,807 Egyptian pound).
- ***Dose***; **0.5 mg** ***once*** a **day**.
Side effects; **# # # # # # # PATIENT COUNSELLING # # # # # # #**
  # **Bradycardia**; ECG monitoring is recommended within 6 months.
  # **First-** and **second-degree atrioventricular block**.
  # **Hypertension**; Blood pressure monitoring during treatment.
  # **Lymphocytopenia**; Risk of infections; herpes virus infection, CBC monitoring.
  # **Macular edema** (edema in the macula of the retina); Ophthalmologic examination is needed before and 3-4 months after drug therapy.
  # **Respiratory effects**; decrease FEV_1 and diffusion lung capacity for carbon monoxide.
  # **Liver effects**; Elevations of liver enzymes.

- ***Contraindications***; ######## **PATIENT COUNSELLING** ########

- ***Patients with*** **myocardial infarction, unstable angina, stroke, transient ischemic attack (TIA), decompensated heart failure** or **second-** or **third-degree atrioventricular block.**
- ***Pregnancy***; ***Avoid*** **(Category C)** ***during*** **treatment** & for **2 months** ***after*** **treatment.**
- ***Avoid*** **live attenuated vaccines** (vaccines less effective during and 2 months after drug treatment).

Teriflunomide (Aubagio®)#

Teriflunomide is the ***active metabolite*** of Leflunomide.
Leflunomide (Arava®) is a **DMARD** ***used in*** **rheumatoid arthritis.**
Teriflunomide was ***approved by*** the **FDA** in **2012** for the ***treatment of patients with*** **relapsing forms of MS**, the **treatment cost** is ***very expensive*** (price *higher than* GILENYA®).
- ***Half life***; ***Long*** **half-life** (8-19 days); ***about*** 3 months to reach steady-state concentrations; ***about*** 8 months to eliminate drug and may take up to 2 years.
- ***Dose***; 7 mg or 14 mg once daily.
- ***Most common side effects***; **Hepatotoxicity, Teratogenic** ***effect*****, GI** ***effects*** **(diarrhea** and **nausea), dermatologic** ***effects*** **(alopecia** and **rash), Hypertension, Neutropenia** and **lymphopenia** (***risk of infection***, ***particularly*** **TB infections**).
- ***If women*** **planning** to be **pregnant**, she ***must be*** **discontinue the drug** and ***insure*** the **plasma concentrations** of Teriflunomide less than 0.02 mg/L.
- **FDA black box warning**; ***risk of*** **hepatotoxicity** and **teratogenicity (category X).**

Natalizumab (Tysabri®)#

Natalizumab is a ***humanized*** **monoclonal antibody** ***against*** the **α-4 subunit of integrin molecules**, ***used*** in the ***treatment of*** **multiple sclerosis** and **Crohn's disease.**
- ***Indication in MS*** as a ***monotherapy*** for the treatment of **patients** ***with*** **relapsing forms of MS.**
- ***Dose in MS***; **300 mg** ***IV infusion*** *over* **1 hour** *every* **4 weeks**, the **treatment cost** is ***very expensive*** (price *higher than* previous drugs).
- **Side effects/Precautions**;
  - **Progressive Multifocal Leukoencephalopathy**; **PML** (viral CNS infection, John Cunningham virus; JCV); rapidly progressive and usually results in death or permanent disability. The ***risk of PML***; **1**) history of previous immunosuppression. **2**) Long duration of Natalizumab treatment, beyond 2 years. **3**) JC virus antibody positivity.
  - ***Common side effects***; **hypersensitivity reactions** (low risk of anaphylaxis), **fatigue, headache** and **nausea.**
  - **Antibodies formation** to Natalizumab (9-10%), *associated with* ***increased*** **relapses** and **hypersensitivity reactions.**

Mitoxantrone (Novantrone®)#

- Mitoxantrone is an ***antineoplastic agent***.
Indication in MS; In ***secondary*** **progressive** or **relapsing-remitting MS.**
- ***Dose in MS***; 12 mg/m^2 IV infusion every 3 months (max. lifetime dose: 140 mg/m^2).
- ***Because*** of the ***potential for*** **toxicity**, Mitoxantrone is ***used only*** patients with ***advancing*** **MS** who's ***other therapies*** have **failed.**
- ***Toxicity***; Cardiotoxicity (risk for heart failure, ECG monitoring must be performed) and leukemia.
- ***Pregnancy***; ***Avoid*** **pregnancy (Category D).**
- ***Precautions***; **laboratory tests** (CBC, bilirubin, liver enzymes, alkaline phosphatase and pregnancy test) ***must be*** **performed** ***before*** **each infusion.**

Alemtuzumab (Lemtrada®)#

- **Alemtuzumab** is a ***recombinant*** **monoclonal antibody** ***against*** **lymphocyte antigen** (CD52), it is used in the ***treatment*** of certain types of **lymphocytic leukemia**.

In 2014, **FDA approved Alemtuzumab (Lemtrada®)** for the ***treatment of*** **relapsing forms of MS**.

Indication in MS; ***Patients with*** **relapsing forms** of **MS**, ***generally*** who have had an ***inadequate*** **response** to **2** or **more** ***other*** **medications**.

- ***Dose in MS***; it is administered as ***2 separate*** **courses** (the **treatment cost** is ***very expensive***);
  - **First treatment course**: 12 mg/day IV infusion on 5 consecutive days (60 mg total dose).
  - **Second treatment course**: 12 mg/day IV infusion on 3 consecutive days (36 mg total dose) given 12 months after the first treatment course.
- **Risk Evaluation Mitigation Strategy (REMS) program**; the drug ***must be*** **registered** in a **REMS monitoring program**, ***because of*** the **risk of autoimmunity** (serious, sometimes fatal; such as immune thrombocytopenia), **infusion reactions** (such as anaphylaxis) and **malignancies** (increased risk of malignancies, including thyroid cancer and melanoma).

II) Symptomatic Therapies

Fatigue

Amantadine (PK-Merz®), **Methylphenidate (Ritalin®)** and **Fluoxetine (Prozac®)**.

Pain

Tricyclic antidepressants; are ***first-line drugs*** for **primary pain**.

Anticonvulsants; **Carbamazepine**, **Phenytoin** & **Gabapentin** as ***second-line agents***.

NSAIDs or **other analgesics** can be used in secondary pain.

Spasticity (Muscle tone caused by brain or spinal problems)

First line; **Baclofen (Lioresal®)** and **Tizanidine (Sirdalud®)**; *skeletal muscle relaxant*

Second line; **Dantrolene (Dantrium®)**, direct muscle relaxant, **Diazepam (Valium®)**.

Third line; ***Intrathecal*** **Baclofen**.

Focal spasticity; **Botulinum toxin (Botox®)**.

Walking Impairment

Dalfampridine (Ampyra®)

It is the ***only*** **medication** ***approved by*** the **FDA** in 2010 for ***improvement of*** **walking** in **patients** with **multiple sclerosis**.

- ***Dose***; 10 mg orally twice daily.
- ***Most common side effects***; **seizures**, **urinary tract infections** and **insomnia**.
- ***Warnings/Precautions***; **Anaphylaxis**, **Seizures** (dose-dependent) & **urinary tract infection**.

Pseudobulbar Affect (PBA); Emotional Mismatch

Dextromethorphan/Quinidine (Nuedexta®)

Dextromethorphan; is a cough suppressant drug, **Quinidine**; is an antiarrhythmic drug.

Nuedexta® contain **20 mg Dextromethorphan Hydrobromide** and **10 mg Quinidine Sulfate**.

Antiepileptic Drugs

➢ Classification of Seizures:-

A) Focal-Onset Seizures

* Is a seizure, which the **electrical disturbances** is ***focused*** in just **one part** of the **brain**.

1) Simple Focal Seizures

* ***Affect only*** a **small region** *of the* **brain**.
* **Preserved consciousness**.

2) Complex Focal Seizures

* ***Usually*** **start** in a **small area**, then ***quickly*** involve **other areas** of the brain.
* **Some alteration** or **impairment of consciousness**.
- ***Typically last*** **30 sec**. to **2 min**., ***but*** may feel tired for several hours after attack.
- **Motor behaviour aura** ***called*** **automatisms** (such as finger rubbing, lip smacking, chewing or swallowing or sleepwalking).
- The ***abnormal*** **electrical activity** might ***spread to*** cause a **secondary generalized seizures**.

3) Secondarily Generalized Seizures

- ***Often*** **begin** with an **aura** (warning sign) ⇨ ***then into*** a **generalized tonic-clonic convulsion**.

B) Generalized-Onset Seizures

* Is a seizure, which the **electrical disturbances** found in the **whole** or a **larger portion** of brain.
* ***Impair*** in **consciousness**.

1) Generalized Tonic-clonic Seizures

* The ***old term*** is **grand mal** [grahn-mahl] **seizures** (*from the French* "**great illness**").
* ***Typically*** **last 1-3 minutes**.
- A **tonic-clonic seizure** ***comprises*** **two main phases**;
  * **Tonic phase** (*comes first and short*); ***Quick*** **loss of consciousness** ⇨ ***falls*** to the **floor** ⇨ ***suddenly*** **muscles tension** (**stiffness**); body flexion and extremities pulled towards the body (***may*** **cry out** *due to* **air** is ***forced from*** the **lungs** and ***may*** **turn blue** in **face**).
  * **Clonic phase**; The **arms** and *usually* the **legs** begin to **jerk** ***rapidly*** and **rhythmically** (**rhythmic** ***jerking***) ⇨ after a ***few minutes***, the **jerking** ***slows*** and **stops**.

2) Absence Seizures

* The ***old term*** is **petit mal** [PET-ee-mahl] **seizures** (*from the French* "**little illness**").
* ***Typically*** begin during **childhood** and ***may persist*** into **adulthood** (***more common*** in **children**).
* ***Short period*** of **impaired consciousness**.
* ***Typically*** **last 10-30 seconds**.
* ***Attack***; *Generally*, ***short period*** of **impaired consciousness** (***only*** **clinical symptom**).
* **Attacks** *may occur* ***up to*** **hundreds** of **times** a **day**.

3) Myoclonic Seizures

* **Myoclonic** [MY-o-KLON-ik] **seizures** are a ***brief*** of **sporadic shock-like jerking** of a **muscles**.
* **Patient** *usually* **awake** and ***able to*** **think** ***clearly***.
* **Jerking movements** ***occurs in*** the **upper** or **lower extremities**, or ***may occur*** in **entire body**.
- They occur in a variety of epilepsy syndromes that have different characteristics

4) Atonic Seizures

* ***Characterized by*** a ***brief loss*** of **muscle tone** and ***falls*** to the **ground** (*known as* **drop attacks**).
- They begin in childhood and may persist into adulthood.

5) Tonic Seizures

* ***Only*** **tonic phase** of a **tonic-clonic seizure**; ***sudden stiffening movements***.

6) Clonic Seizures

* ***Only*** **clonic phase** of a **tonic-clonic seizure**; ***rhythmic jerking muscle movements***.

C) Status Epilepticus (SE)

* **Status Epilepticus** (**SE**) *new definition*; is ***any seizure*** that **lasts** ***more than*** **5 minutes** or ***more than*** **1 seizure** ***within*** a **5 minutes** period ***without returning to*** **normal** ***between*** **them**.

➢ General Mechanism of Action of Antiepileptic Drugs:-

Blocking **voltage-gated channels** (Na^+ or Ca^{2+}).
Enhancing **inhibitory γ-aminobutyric acid (GABA).**
Interfering with **excitatory glutamate transmission.**

- ***N.B.***; **Antiepileptic drugs *suppress* seizures *but* do not "*cure*" or "*prevent*" epilepsy.**
- **Antiepileptic Drugs *Brief History***; In the mid-**1800s**, the first effective anti-seizure medication, **Potassium Bromide**, was introduced. The ***first modern*** treatment, **Phenobarbital**, was developed in **1912**, with **Phenytoin** coming into use in **1938**.

➢ Antiepileptic Drugs:-

Antiepileptic Drugs (AEDs)

I) Sodium Channel Blockers

Hydantoins
Phenytoin (Dilantin®)
Fosphenytoin (Cerebyx®)
Ethotoin (Peganone®)
Mephenytoin (Mesantoin®)

Carboxamides
Carbamazepine (Tegretol®)
Oxcarbazepine (Trileptal®)
Eslicarbazepine Acetate (Aptiom®)

Other Sodium Channel Blockers
Lamotrigine (Lamictal®)
Zonisamide (Zonegran®)
Lacosamide (Vimpat®)
Rufinamide (Banzel®)

II) GABA Enhancing Agents

Barbiturates
Phenobarbital (Luminal®)
Primidone (Mysoline®)

Benzodiazepines
Clonazepam (Rivotril®)
Clobazam (Frisium®)
Lorazepam (Ativan®)
Diazepam (Valium®)

Valproates
Valproic Acid (Depakene®)
Sodium Valproate (Depakine®)
Divalproex Sodium (Depakote®)

Other GABA Enhancing Agents
Vigabatrin (Sabril®)
Tiagabine (Gabitril®)

III) GABA Analogs

Gabapentin (Neurontin®)
Pregabalin (Lyrica®)

IV) Multiple or Other Mechanisms of Action

Felbamate (Felbatol®)	**Topiramate** (Topamax®)	**Perampanel** (Fycompa®)
Ethosuximide (Zarontin®)	**Levetiracetam** (Keppra®)	**Brivaracetam** (Briviact®)
Ezogabine (Potiga®)	**Stiripentol** (Diacomit®)	**Acetazolamide** (Diamox®)

I) Sodium Channel Blockers

Hydantoins

Phenytoin (Dilantin®)# (Epanutin®)#

- ***Routes of administration***; **Oral** (cap, chew tab or susp), **Rectal** and **IV** (IM not recommended).
* **Phenytoin** is an ***inducer*** of the **CYP3A4** and **CYP2C19** families.
# ***Indications***; **Focal** (or **partial**), **generalized tonic-clonic seizures** and **status epilepticus**.
- ***Dose***; **Orally** 200mg - 500mg daily divided into 1 or 2 doses. **IV**; 10-15 mg/kg at 25-50 mg/min.
Side effects;
  * ***Dose-related side effects***; **Nystagmus**, **Diplopia**, **ataxia** & **drowsiness**.
  * ***Non-dose-related side effects*** (***chronic***); **Gingival hyperplasia**, **hirsutism**, **acne**, **rash**, **hepatotoxicity** and **coarsening of facial features** (change in normal facial features).
  - ***Chronic use*** may associated with ***decrease*** **bone mineral density** (*vitamin D metabolism abnormality*) and **megaloblastic anemia**.
  - ***IV infusion side effects***; **phlebitis** and **hypotension** (*with rapid infusion*).
Pregnancy **category D**;
  - **Fetal Hydantoin Syndrome**; **Cleft lip or palate**, **congenital heart disease**, **slowing of growth** and **mental deficiency**.
  - **Life-threatening fetus bleeding**; decrease vitamin K-dependent clotting factors.
- ***Drug interactions***; CYP3A4 *inhibitors or inducers*.
- ***N.B.***; **Phenytoin** (**Healosol®** spray) in **wound healing**; **evidence** ***suggests*** that **topical phenytoin** is ***useful*** in **wound healing** in people with **chronic skin wounds**.

Fosphenytoin (Cerebyx®)

- **Fosphenytoin** is a ***prodrug*** that is ***rapidly converted to*** **Phenytoin** within minutes.
* ***Advantages over phenytoin***;
1) IM dosing and ***more safely*** **IV dosing**. **2) Phlebitis** is ***minimized***.
3) Infusion rate 3 times ***faster*** (150 mg/min). **4)** ***Can*** **deliver** in **normal saline** or **5% dextrose**.
- ***Dose***; 15-20 mg/kg at 100-150 mg/min (1.5 mg of **Fosphenytoin** = 1 mg of **Phenytoin**).
- ***Indications***; ***most commonly*** **used in status epilepticus**.
- ***Side effects***: **Hypotension**, **perianal itching** and ***other side effects*** of **Phenytoin**.

Ethotoin (Peganone®)

- ***Indications***; **used in patients** who are ***hypersensitive*** to **Phenytoin**, ***but*** **less effective**.
- ***Side effects***; ***less severe*** than **Phenytoin** (***lacks of*** **gingival hyperplasia** and **hirsutism**).

Mephenytoin (Mesantoin®)

- It is ***metabolized to*** **Nirvanol**; is ***quite*** **toxic**. **Mephenytoin** is ***no*** **longer available**.

Carboxamides

Carbamazepine (Tegretol®)# (Carbatrol®)

Carbamazepine (**CBZ**) is a ***major most popular first-line antiepileptic drug for*** **focal seizures** and **generalized tonic-clonic seizures**.
Carbamazepine is *closely related to* **Imipramine** and it is a **tricyclic compound** ***effective*** in ***treatment*** **bipolar depression**, the ***value*** in the **treatment of** ***epilepsy*** was ***discovered*** by **chance**.
- ***Mechanism of action***; like **Phenytoin**, ***blocks*** **voltage-gated sodium channels**.
- ***Pharmacokinetics***; **Absorbed** ***slowly*** after **oral administration** and **varies** ***widely*** **among patients**, *but* ***complete*** **absorption** apparently ***occurs in*** **all**.
  * **Carbamazepine** is an ***inducer*** of the **CYP1A2**, **CYP2C**, and **CYP3A**.
- ***Formulations***; **Tegretol®**; **Chewable tablets** 100 mg, 200 mg, **Suspension** 100 mg/5 mL and **Suppositories** 125mg, 250mg. **Tegretol®** CR or XR; **Extended-release tablets** 100 mg, 200 mg & 400 mg (twice). - ***Dose***; 800 mg - 1200 mg divided into 2 or 4 doses.
- ***N.B.***; **Tegretol®** CR or XR, ***must be*** **swallowed whole** and ***never*** **crushed** or **chewed**, while **Carbatrol®** extended-release capsules ***can be*** **opened** and ***sprinkled on*** **food**.

Indications; **Focal, generalized tonic-clonic seizures, trigeminal neuralgia & bipolar disorder.**
* It is *not effective* for **absence seizures** or **myoclonic seizures** (*may increase seizures*).
# *Side effects*;
* *Dose-related side effects*;
- **Diplopia, ataxia, drowsiness** and **mild GI upsets**.
- **Hyponatremia** due to an antidiuretic hormone (ADH)-like effect.
* *Non-dose-related side effects*; **Aplastic anemia, thrombocytopenia** and **leukopenia**.
* *Idiosyncratic side effects*; **skin rash** and **hepatic dysfunction**.
# **FDA Warning**; **Hypersensitivity Reactions, HLA-B*1502** and **HLA-A*3101 Alleles**
- *Drug interactions*; **CYP3A4** *inhibitors or inducers*.

Oxcarbazepine (Trileptal®)# (Oxtellar® XR)#

Oxcarbazepine (**OXC**) is a ***prodrug*** that is ***rapidly reduced*** to the **active monohydroxy** (**MHD**) **metabolite derivatives** (***R*-licarbazepine** and ***S*-licarbazepine**).
Formulations; - **Trileptal®**; tablets 150 mg, 300 mg, 600 mg and suspension 60 mg/ml.
- **Oxtellar® XR**; extended-release tablets 150 mg, 300 mg, 600 mg.
- *Dose*; 600 mg - 2400 mg daily divided into 2 or 3 doses.
Indications; ***Approved*** as ***monotherapy*** or ***adjunctive therapy*** in ***patients with* partial seizures**.
Off-label; **Bipolar disorder, diabetic neuropathy** and **trigeminal neuralgia**.
- **Oxcarbazepine** and **MHD** are **CYP3A4 & CYP3A5** ***inducers***, (***less potent than* Carbamazepine**).
- *Side effects*;
* **Hyponatremia** ***more common*** *than* with **Carbamazepine** (***increased with* dose & age**).
- **Hematologic** ***side effects less common*** *than* with **Carbamazepine**.
- **Hypersensitivity** ***less common*** *than* with **Carbamazepine** (25-30% of patients with hypersensitivity to **Carbamazepine** will have hypersensitivity to **Oxcarbazepine**).
- *Drug interactions*; **CYP3A4** *inhibitors or inducers*.

Eslicarbazepine Acetate (Aptiom®)

Eslicarbazepine (**ESL**) **Acetate** is a ***prodrug*** that is ***converted to*** the **active metabolite Eslicarbazepine** (***S*-licarbazepine**). ***S*-licarbazepine** is ***active metabolite*** of **Oxcarbazepine**.
- *Indications*; **Eslicarbazepine** is ***similar to* Oxcarbazepine**. The ***possible advantage*** of **Eslicarbazepine** is ***linear pharmacokinetics*** and ***dose*** is **once daily**.
- *Formulations*; **Aptiom®**; tablets 200 mg, 400 mg, 600 mg, 800 mg.
- *Side effects*; **Dizziness, somnolence, nausea, headache** and **diplopia** (**Hypersensitivity** and **hyponatremia** are ***less common***).

Other Sodium Channel Blockers

Lamotrigine (Lamictal®)#

- It is ***metabolized predominantly*** by **glucuronic acid *conjugation***.
Formulations; - **Lamictal®** tablets; 25 mg, 100 mg, 150 mg, 200 mg.
- **Lamictal®** XR; 25 mg, 50 mg, 100 mg, 200 mg, 250 mg, 300 mg.
- **Lamictal®** Chewable/dispersible tablets; 2 mg, 5 mg, 25 mg.
- **Lamictal®** Disintegrating tablets; 25 mg, 50 mg, 100 mg, 200 mg.
Indications; ***Monotherapy*** or ***adjunctive therapy*** in **partial, generalized, absence, myoclonic seizures, Lennox-Gastaut syndrome *associated seizures*** and **bipolar disorder**.
Off-label; **Peripheral neuropathy, trigeminal neuralgia, cluster headaches, migraines** and ***many* psychiatric disorders**.
* *Side effects* (**FDA *warning***); ***Risk of* skin rash** (**Stevens-Johnson syndrome** and **toxic epidermal necrolysis**), which may be ***life-threatening* reaction**.
* ***N.B.***; * **Estrogen** (in ***oral contraceptives***) ***increase* Lamotrigine clearance**, so ***twice*** the **amount** of **Lamotrigine *may be* necessary**.
* **Valproic acid *decreases* Lamotrigine metabolism** and ***dose adjustment*** is **required**.

Zonisamide (Zonegran®)

Zonisamide is a ***sulfonamide anticonvulsant*** with ***weak*** **carbonic anhydrase inhibitor** ***effect***.
- ***Indications***; *Approved by* **FDA** *for* used as ***adjunctive therapy*** in ***patients with*** **focal seizures**.
- ***Dose***; 100 mg - 600 mg/d in adults and 4 mg to 12 mg/d in children.
- ***Side effects***; **Drowsiness, cognitive impairment** and **skin rashes** (*sulfa allergies*).

* ***N.B.***; ***Concomitant use*** of **Zonisamide** and ***other*** **carbonic anhydrase inhibitors** such as **Topiramate** and **Acetazolamide**, ***increase*** the potential for **metabolic acidosis**.

Lacosamide (Vimpat®)

- ***Indications***; *Approved* as ***monotherapy*** and as ***adjunctive therapy*** for **adolescents 17 years** and **older** with **partial-onset seizures**.
- ***Side effects***; **Dizziness, ataxia, vomiting** and **diplopia**.
- ***Warning***; **Suicidal ideation, arrhythmia** and **hypersensitivity reactions**.

Rufinamide (Banzel®)

- ***Pharmacokinetics***; **Absorption** ***increased by*** **food**.
- ***Indications***; It was ***approved by*** the **US FDA** in **2008** as ***adjunctive treatment*** of ***seizures associated*** with **Lennox-Gastaut syndrome**.
- ***Side effects***; **Somnolence, vomiting, fatigue, diarrhea** and **QT interval** ***shortening***.

II) GABA Enhancing Agents

Barbiturates

Phenobarbital (Luminal®)#

Currently, its **use** is ***limited*** *because* of its **adverse effects**.
Phenobarbital is a ***powerful*** **inducer** of the **hepatic microsomal enzymes** (**Enzyme Inducing Antiepileptic Drugs**; **EIAEDs** ***such as*** **Phenytoin, Carbamazepine** and **Phenobarbital**.
- ***Indications***; *Usually in* **status epilepticus** (***emergency***), ***when*** **other agents** ***fail***.

Primidone (Mysoline®)

- **Primidone** (**Desoxyphenobarbital**) is ***metabolized*** to **Phenobarbital** (*major*) and **Phenylethylmalonamide**, ***all three compounds*** are **active anticonvulsants**.
- ***Indications***; **Partial** and **generalized tonic-clonic seizures**,
- ***History***; **Primidone** was once a ***primary*** **anticonvulsant** in the treatment of **partial** and **generalized seizures** and was the ***treatment of choice***, *especially* when ***combined with*** **Phenytoin**, ***but*** in early **1980s**, **Carbamazepine** had ***surpassed*** **Primidone** ***popularity***.

Benzodiazepines (BDZs)

Clonazepam (Rivotril®)#	**Clobazam** (Frisium®)#
Lorazepam (Ativan®)#	**Diazepam** (Valium®)#

- ***Most commonly used***; **Clonazepam** (stronger), **Lorazepam** (longer) and **Diazepam** (faster).
- **Clobazam** is ***widely used*** by **specialist epilepsy clinics** ***worldwide***.
- **Clonazepam** is ***most*** **popular**.
- ***Indications***; *Usually used as* **adjunctive, short-term therapy** (***emergency***).

Valproates (VPAs)

Valproic Acid (Depakene®)#	**Sodium Valproate** (Depakine®)
Divalproex Sodium (Depakote®)	

- **Valproates** was ***first made*** in **1882** and came into ***medical use*** in **1960s**.
- **Valproic Acid** is a ***fatty carboxylic acids***.

Divalproex Sodium is a ***combination*** of **Sodium Valproate** ***and*** **Valproic Acid** that is ***converted to*** **Valproate** when it reaches the **GIT**, ***All*** of this **forms** are ***equivalent*** in **efficacy**.
Formulations; **Valproates** are ***available*** in **multiple-salt dosage forms** and ***extended-release*** **formulations** (**Depakine® Chrono**).

Indications; **Valproates** are ***very effective against*** **absence seizures**, **myoclonic seizures** and **tonic-clonic seizures**. ***Dose***; 1000 mg - 2000 mg daily divided into 1 or 2 doses.
- ***Other uses***; **Bipolar disorder** and **migraine prophylaxis**.
- ***Most common side effects***; **Nausea**, **vomiting** and **drowsiness**.
FDA Warning; **Fatal hepatotoxicity** (liver enzyme monitoring is needed within the first 6 months), **Severe birth defects** (Spina bifida and lower intelligence quotient; IQ), **fatal pancreatitis** and **suicidal ideation**.
- ***Drug interactions***; **Phenobarbital**, **Phenytoin**, **Carbamazepine**, **Oxcarbazepine** and **Primidone**.

Other GABA Enhancing Agents

Vigabatrin (Sabril®)#

Indications; **Partial seizures** and **infantile spasms** (*rare epileptic disorder in infants*).
- ***Dose***; 2000-3000 mg/d divided into 1-2 doses, **infant**; 50-150 mg/kg/day in 2 divided doses.
Side effects; **drowsiness**, **dizziness**, **blurred vision** and **weight gain**.
FDA Warning; **Vision loss** (*long-term therapy*) from mild to severe in 30% or more of patients.

Tiagabine (Gabitril®)#

Indications; *approved by* FDA; ***adjunctive treatment*** for **partial seizures** in **ages 12 *and* up**.
Off-label; **Anxiety disorders** and **neuropathic pain**.
- ***Side effects***; **Dizziness**, **paresthesia**, **nervousness**, **tremor** and **depressed mood**.

III) GABA Analogs

Gabapentin (Neurontin®)#

Gabapentin is an ***analog*** (***analogue***) ***of*** **GABA**, it was *developed to* have a **structure** ***similar*** to that of **GABA**; however, ***in fact***, **little** or **no action** on the **GABA receptor** or ***enhance*** **GABA actions**, it was originally ***approved by*** the U.S. FDA in **1993**, for use as an ***adjunctive treatment*** for **partial seizures** in **adults**.
Gabapentin has ***anticonvulsant***, and ***anxiolytic effects***.
- ***Pharmacokinetics***; **Absorption** is ***nonlinear***, ***not*** **metabolized** and **eliminated unchanged** ***renally*** (dose adjustments in renal dysfunction).
Indications; ***adjunctive treatment*** for **focal-onset seizures** and **postherpetic neuralgia** (neuropathic pain following shingles; herpes zoster virus).
- ***Dose***; 900 mg - 3600 mg daily divided into 3 doses.
Another formulations; - **Gabapentin** (**Gralise®**) ***extended-release*** **tablets** 300 and 600 mg, ***indicated only*** for **postherpetic neuralgia** ***not*** **epilepsy**.
- **Gabapentin Enacarbil** (**Horizant®**) ***extended-release*** **tablets** 300 and 600 mg, is a ***prodrug*** for **Gabapentin** and is ***indicated for*** **postherpetic neuralgia** and **restless legs syndrome**, ***not*** **epilepsy**.
- ***Side effects***; **Dizziness**, **fatigue**, **drowsiness**, **ataxia**, **nystagmus** and **tremor**.
- ***Drug interactions***; *Negligible*.

Pregabalin (Lyrica®)#

Pregabalin is a ***structural analogue of*** **GABA**, has ***analgesic***, ***anticonvulsant*** and ***anxiolytic effects***, it was ***approved by*** the U.S. FDA in **2004**.
Pregabalin (**Lyrica®**) is ***one*** of the **top 10** ***most seller*** **drugs** ($3.4 billion in 2015).
- ***Pharmacokinetics***; like **Gabapentin**, ***not*** **metabolized** and **eliminated** ***renally*** (dose adjustments in renal dysfunction).
Indications; ***adjunctive treatment*** for **focal-onset seizures**, **diabetic peripheral neuropathy**, **postherpetic neuralgia**, **fibromyalgia** & **neuropathic pain** ***associated with*** **spinal cord injury**.
- ***Dose***; 300 mg daily divided into 2-3 doses.
- ***Side effects***; **Drowsiness**, **blurred vision**, **weight gain** and **peripheral edema**.
N.B; **Pregabalin** is ***classified as*** **Schedule V controlled substance** in **US**, ***abrupt discontinuation***, may cause ***withdrawal symptoms***; **insomnia**, **nausea**, **headache** & **diarrhea**.

IV) Multiple or Other Mechanisms of Action

Felbamate (Felbatol®)#

- Felbamate is a *potent anticonvulsant*, *very effective against* multiple seizure types.
Indications; It is reserved for use in refractory epilepsies (*particularly* Lennox-Gastaut syndrome) *because of* the *risk of* aplastic anemia and hepatic failure.

Topiramate (Topamax®)#

- Topiramate is a *fructose derivative*, *was developed as* an antidiabetic drug, *but* it was found to have *very potent anticonvulsant effects*.
- *Pharmacokinetics*; *Not* metabolized and eliminated unchanged *renally*.
Indications; Partial & generalized tonic-clonic seizures, Lennox-Gastaut syndrome, migraine prophylaxis, *in 2012*, it was approved in *combination with* Phentermine for weight loss.
- *Side effects*; Somnolence, paresthesia, cognitive slowing, confusion, weight loss, renal stones, glaucoma, oligohidrosis (*decreased sweating*) and hyperthermia.

Perampanel (Fycompa®)

- *Pharmacokinetics*; *Long* half-life (*once-daily*),
- *Indications*; *In 2012*, US FDA *approved* Perampanel as *adjunctive treatment* for partial-onset seizures; *in 2015* as *adjunctive treatment* for primary generalized tonic-clonic seizures.
- *Side effects*; Dizziness, *aggressive behaviour* (irritability, aggression, anger, anxiety), drowsiness and headache.
- *Warning*; *Serious* or *possibly* life-threatening mental, mood or behaviour problems, Perampanel is designated as a Schedule III controlled *substance*.

Ethosuximide (Zarontin®)

Ethosuximide is a *succinimide anticonvulsant*, it was introduced in 1960s.
Mechanism of action; *blocking* T-type Ca^{2+} channels receptors.
Indications; *Only* effective in *treating* absence seizures.
- *Side effects*; Gastric distress, nausea and vomiting.

Levetiracetam (Keppra®)#

- Levetiracetam is an *S*-enantiomer of Etiracetam, it is a Piracetam *analog*.
* *Pharmacokinetics*; *Not* metabolized & eliminated unchanged *renally* (*No* drug interactions)
- *Indications*; *Adjunctive* for focal, myoclonic, and primary generalized tonic-clonic seizures.
- *Off-label*; Status epilepticus (*parenteral formulation*).
- *Side effects*; Somnolence, asthenia, ataxia and dizziness.

Brivaracetam (Briviact®)

- It *was approved* in February 19th, 2016 as *adjunctive treatment* of partial-onset seizures.

Ezogabine or Retigabine (Potiga®)

- Ezogabine is a *unique anticonvulsant* (*novel mechanism*), it *was approved* in 2011.
- *Mechanism of action*; Potassium channel *opener*.
- *Indications*; *Adjunctive* for partial-onset seizures. - *Dose*; 600-1200 mg/d divided into 3 doses.
- *Off-label*; Tinnitus.
- *Side effects*; Urinary retention, QT interval *prolongation*, blue skin discoloration and retinal abnormalities.
- *N.B.*; Ezogabine is *classified as* Schedule V controlled substance.

Stiripentol (Diacomit®)

- *Indications*; *With* Clobazam and Valproate in the *adjunctive therapy* of *refractory* generalized tonic-clonic seizures in patients *with* severe myoclonic epilepsy of infancy (SMEI, Dravet's syndrome). *Dose*; 50mg/kg/day divided into 2-3 doses.
- *Side effects*; Nausea, vomiting, aggression and ataxia *due to* Stiripentol (*potent inhibitor* of CYP3A4, CYP1A2 and CYP2C19) *increase* concentrations of Clobazam and Valproate.

➢ Medication Selection for Various Seizure Types:-

Drug	Focal	Gen. Tonic-Clonic	Absence	Atypical Absence	Atonic	Myoclonic	Infantile Spasms	Status Epilepticus	Lennox-Gastaut Syndrome
Na Ch. Blocker									
Phenytoin			–	–	–		–		–
Carbamazepine			–	–			–	–	–
Oxcarbazepine			–	–			–	–	–
Eslicarbazepine		–	–	–	–	–	–	–	–
Lamotrigine							–	–	
Zonisamide				–	–		–	–	–
Lacosamide		–	–	–	–	–	–		–
Rufinamide				–		–	–	–	
GABA Enhancing									
Phenobarbital				–	–		–		–
Primidone				–	–	–	–	–	–
Clobazam				–	–		–	–	
Clonazepam								–	
Lorazepam					–		–		–
Diazepam	–	–	–		–				
Valproic Acid									–
Vigabatrin			–	–	–	–		–	–
Tiagabine		–	–	–			–	–	–
GABA Analogs									
Gabapentin			–	–	–	–	–	–	–
Pregabalin		–	–	–	–	–	–	–	–
Multiple or Others									
Felbamate				–	–		–	–	
Topiramate				–			–	–	–
Perampanel		–	–	–	–	–	–	–	–
Ethosuximide	–	–			–		–	–	–
Levetiracetam				–	–		–		–
Ezogabine		–	–	–	–	–	–	–	–
Acetazolamide					–	–	–	–	–

- *Colour Guide*;

First-line drug
Second-line drug
May be used
Adjunctive treatment
Only when benefits outweigh risks

Table from American College of Clinical Pharmacy (ACCP) Updates in Therapeutics 2015

- **Newly diagnosed epilepsy**; First line drug ⇨ If seizures persist ⇨ Second line drug ⇨ If seizures persist ⇨ Adjunctive therapy ⇨ If seizures persist ⇨ Vagal nerve stimulation

Headache Managements

	Migraine	Tension Headache	Cluster Headache
Pain	Pulsating or Throbbing	Pressing or Tightening	Sharp or Stabbing
Pain Intensity	Moderate to Severe	Mild to Moderate	Severe to Very severe
Duration	4 hours to 3 days	30 min. to several days	15-180 minutes
Location	Unilateral or Bilateral	Bilateral	Unilateral, eye focused
Aura	With or Without	Without	Without
Nausea/Vomiting	Very common	No	No
Photophobia or Phonophobia	Very common	No more than one	No (running nose and tears are common)

Migraine

➢ Symptoms and Signs:-

- **Typical symptoms** of **migraine** ***include the following***: (TV-ON-SD)

Throbbing (Pulsating) Pain	- Pain with each beat of the heart, with moderate to severe.
Visual Disturbances "Aura"	- Visual disturbances are considered a common warning sign of classical migraine (migraine with aura; MWA, *see next*).
One Sided Head Pain	- Most of patients feels; one-sided head pain (unilateral). - *Some* of patient feels; pain on both sides, in their neck, or at the front or back of their head (bilateral).
Nausea or Vomiting	- Nausea (80%) and vomiting (50%) are very common.
Sensitivity to Light and Sound	- Sensitivity or aversion to light and sound is one of the most common signs of migraine.
Dizziness	- Dizziness is common.

➢ Migraine Triggers:-

Hormonal	Lifestyle	Foods
Menstruation Pregnancy Menopause	Smoking Emotional stress Sleep disturbances Not eating or skipping meals	Caffeine Chocolate Alcohol (Red wine) Aspartame (sweetener) Aged cheese (tyramine food) Monosodium glutamate (MSG) Ice cream (*ice not cream*) Smoked fish and meats Processed meat Citrus fruits Onions, Nuts Avocados, Tomatoes,

Environmental	Medications
Bright, flash or fluorescent light Strong odour (perfumes) Weather changes	Oral contraceptives Vasodilators

➢ **Managements:-**

Acute Attack Treatment

Triptans		
Sumatriptan (Imitrex®)#	**Zolmitriptan** (Zomig®)#	**Rizatriptan** (Maxalt®)
Naratriptan (Amerge®)#	**Eletriptan** (Relpax®)#	**Almotriptan** (Axert®)
Frovatriptan (Frova®)		

- They are ***selective* agonists** for **5-HT_{1B}** and **5-HT_{1D}** receptors.

Triptans are a family of tryptamine-based drugs, introduced in the 1990s for the ***treatment*** of **migraines** and **cluster headaches**.

All of these agents available in **oral preparation**, **Sumatriptan** available in **nasal**, **SC** and **rectal *preparation***, **Zolmitriptan** available in **nasal *preparation***, **Zolmitriptan** and **Rizatriptan** are available in an **oral disintegrating tablet**.

There is also a ***combination preparation*** of **triptan/nonsteroidal anti-inflammatory (NSAIDs)**; **Sumatriptan/Naproxen** (**Treximet®**), ***indicated for*** the ***acute treatment*** of **migraine with** or **without aura**, and more ***effective*** in **menstrual migraine**.

- ***Contraindication***; Patients with **coronary artery disease**, **stroke**, **uncontrolled hypertension**, **peripheral vascular disease** & **pregnancy** (**Category C**; when benefits outweigh the risks).
- **Serotonin syndrome**; **Triptans** with **SSRIs**, **MAOIs**, or other **antidepressant drugs** (**TCAs**).
- ***Dose***; - ***General Principles***; # # # # # # # # **PATIENT COUNSELLING** # # # # # # # #

* **One dose** for **early/mild headache**.
* ***May be* repeated *after* two hours**.
* **Do not use *more than* two doses** within a **24-hours**.
* **Do not use *more than* 2-3 days *weekly***.
* **NSAIDs, opioids & antiemetics *may*** be **used *with* triptans**.
* **Ergot alkaloids *cannot*** be **taken** on the **same day *with* triptans**.

Triptans	Dosage Forms	Maximum Daily Dose
Sumatriptan (Imitrex®)	Tablets; 25 mg, 50 mg, 100 mg	200
	SC injection; 4 mg, 6 mg	12
	Intranasal; 5 mg, 20 mg	40
Zolmitriptan (Zomig®)	Tablets 2.5 mg, 5 mg	10
	Disintegrating tab.; 2.5 mg, 5 mg	10
	Intranasal 2.5 mg, 5 mg	10
Rizatriptan (Maxalt®)	Tablets; 5 mg, 10 mg	30
	Disintegrating tab.; 5 mg, 10 mg	30
Naratriptan (Amerge®)	Tablets; 1 mg, 2.5 mg	5
Eletriptan (Relpax®)	Tablets; 20 mg, 40 mg	80
Almotriptan (Axert®)	Tablets; 6.25 mg, 12.5 mg	25
Frovatriptan (Frova®)	Tablets; 2.5 mg	7.5
Sumatriptan/Naproxen (Treximet®)	Tablets; 85 mg/500 mg	170/1000

Ergot Alkaloids	
Ergotamine (Ergomar®)#	**Dihydroergotamine** (D.H.E. 45®)# (Migranal®)#

- Used in ***acute treatment*** of **migraine** (***should be*** considered for **patients** with **nausea** or **vomiting**).
- **Ergotamine**, it is often ***combined with* Caffeine** to ***facilitate* absorption** of **ergot alkaloids**.
- **Dihydroergotamine** has ***non*-oral administration routes** (SC, IV and intranasal).

- ***Dose***; - **Ergotamine** (**Ergomar**®); **Initial dose**: **2 mg** under the tongue, ***may be*** **repeated** ***after*** **30 minute** (**must** ***not exceed*** **3 tablets** per day; **6 mg**), **total weekly dose**; **10 mg**.
  - **Dihydroergotamine** (D.H.E. 45®) (**Migranal**®);
    - ***Intranasal***; **1 spray** (0.5 mg) into each nostril (**1 mg**), ***may be*** **repeated** ***after*** **15 minutes** (**must** ***not exceed*** **2 mg** per day), the total **weekly dose**; 8 sprays (**4 mg**).
    - ***IV/IM/SC***; **1 mg** after the ***first symptom***, ***may be*** **repeated** ***after*** **1 hour** (**must** ***not exceed*** **3 mg** per day), the ***total*** **weekly dose**; **6 mg**.
- ***Contraindication***; Patients with **coronary artery disease**, **stroke**, **uncontrolled hypertension**, **peripheral vascular disease** & **pregnancy** (**Category X**).
- ***Drug interactions***; with **potent CYP3A4 inhibitors**, ***elevates*** the **serum levels** of **Ergotamine**, increase ***risk for*** **vasospasm**; **cerebral ischemia** and/or **ischemia** *of the* **extremities**.

Analgesics

- **Non-Steroidal Anti-Inflammatory**; **NSAIDs** (**Simple Analgesics**);
  - # For ***only*** ***moderate*** **migraine attacks** ***not associated with*** **vomiting** or **severe nausea**, **NSAIDs** (*include* **Paracetamol**) or **combination analgesics** are ***first choice agents*** because they are ***effective***, ***less expensive***, and ***less side effects*** than triptans or ergots.
  - # When ***moderate*** **attacks** are ***associated with*** **severe nausea** or **vomiting**, an **oral** or **rectal antiemetic drug** can be **used in** ***conjunction with*** **NSAIDs**.
- **Opioid Analgesics**; **Opioids** and **Barbiturates** ***should not be used*** for the ***treatment*** of **moderate** to **severe migraine**, ***except*** as a **last resort**, due to their ***potential for*** **tolerance** and **dependence**.

Antiemetics

- **IV Metoclopramide**, and **IV** or **IM Chlorpromazine** and **Prochlorperazine** can be ***used as*** **monotherapy** for **acute migraine headache**, act as **antiemetics** ***mainly*** because they are dopamine antagonists. In addition, they are ***effective*** for ***reducing*** **migraine headache pain**.
- **Oral antiemetics** ***should not be considered as*** **monotherapy** in **acute migraine**, **used in** ***adjunctive therapy*** (**Metoclopramide**) with **NSAIDs** to ***decrease*** **nausea** and **vomiting**.

Other Agents

- **Isometheptene**; is a ***sympathomimetic amine*** sometimes ***used in*** **combination** in the **treatment of migraines** due to its ***vasoconstricting properties***.

Combinations

- ***Common Combination Egyptian Brands***;
  - # **Migracid**®; **Paracetamol** + **Metoclopramide**.
  - # **Amigraine**®; **Ergotamine** 1mg + **Caffeine** 100mg + **Metamizole** (or **Analgin** *like NSAIDs*) 300mg.
  - # **Metograine**®; **Ergotamine** 1mg + **Paracetamol** 325mg + **Caffeine** 100mg + **Metoclopramide** 5mg.
  - # **Migrainil**®; **Ergotamine** 1mg + **Meprobamate** (*like Barbiturates*) 150mg + **Metamizole** 200 mg + **Pentobarbital** 10 mg + **Caffeine** 50mg.
- ***Common Combination World Brands***;
  - # **Tylenol**® **No.3**; **Acetaminophen** 300mg (***Paracetamol*** *name in USA*) + **Codeine** 15, 30, 60mg.
  - # **Midrin**®; **Acetaminophen** 325mg + **Isometheptene** 65mg + **Dichloralphenazone** 100mg.
  - # **Fiorinal**®; **Butalbital** (*Barbiturates*) 50mg + **Aspirin** 325mg + **Caffeine** 40mg.
  - # **Excedrin**® **Migraine**; **Acetaminophen** 250mg + **Aspirin** 250mg + **Caffeine** 65mg.

Status Migrainosus

Status Migrainosus: **Attack** of **migraine**, with **headache phase** ***lasting more than*** **72 hours** ***despite treatment***. **Headache-free intervals** of ***less than*** **4 hours**.

- Patients need to be ***hospitalized*** for a short period and may need to be treated with ***intravenous*** **Valproate** or **Dihydroergotamine** or **Corticosteroids** for a **few days**.

Migraine Prophylaxis

*** High efficacy
** Low efficacy
* Limited efficacy

A) **Antihypertensives**; **Beta Blockers** (**Propranolol***** and **Timolol***), **Calcium Channel Blockers** (**Verapamil**** and **Flunarizine***), **Centrally Acting Agents** (**Clonidine****) **ACEIs** (**Lisinopril***), **Angiotensin-Receptor Blockers** (**Candesartan***).
B) **Antiepileptics**; **Valproate***, **Topiramate***, **Lamotrigine****, **Gabapentin***, **Oxcarbazepine***.
C) **Antidepressants**; **TCAs** (**Amitriptyline***, **Nortriptyline***, **Doxepin*** **Protriptyline***), **SSRIs** (**Paroxetine***, **Fluoxetine*** and **Sertraline***).
D) **Serotonin Antagonists**; **Methysergide***, **Pizotifen*** and **Cyproheptadine****.
E) **Botulinum Toxin**; ***Clostridium botulinum*** **toxin type A** *** (Botox®) *Approved*.
F) **Devices**; **TENS** (Transcutaneous Electrical Nerve Stimulation) **device*** (Cefaly® device), *Approved*.

Tension-type Headache (TTH)

Acute Attack Treatment

A) **Simple Analgesics**; *such as* **Aspirin**, **Ibuprofen**, and **Paracetamol**.
B) **Analgesic/combinations**; are ***widely used***.

Prophylaxis Medications

- **Tricyclic Antidepressants**; **Amitriptyline** and **Nortriptyline** are the most commonly used.
- **Evidence** is ***insufficient*** for use; **SSRIs**, **Propranolol** & ***Clostridium botulinum*** **toxin type A**.

Cluster Headache (CH)

Acute Attack Treatment

A) **Oxygen**; **100%** via ***non-rebreather*** **face mask** at 12 to 15 L per minute for 15 to 20 minutes, ***relieves*** **pain** in **50-85%** of **patients**.
B) **Triptans**; SC and ***intranasal*** **Sumatriptan** and ***intranasal*** **Zolmitriptan** are **effective**. **Oral formulations** usually ***do not act quickly enough***, ***but*** **oral** **Zolmitriptan** showed ***efficacy*** in **one trial**.
C) **Intranasal Lidocaine**; **20-60 mg** as a **nasal drop** or **spray** (1 mL of 10% solution applied bilaterally with a cotton swab for five minutes).
D) **Octreotide** (**Somatostatin** ***analogues***; **growth hormone** ***inhibitor***), 100 mcg SC have been used.

Prophylaxis Medications

A) **Verapamil**; 240 mg orally per day, in single or divided doses.
B) **Steroids**; oral **Prednisone** 50-80 mg/d, tapered gradually 10-12 days or sub-occipital injection of **Betamethasone** (used until other drug take effect).
C) **Antiepileptics**; **Valproate** and **Topiramate** are effective.
D) **Melatonin** is effective.

General Anesthetics

Inhalation Anesthetics

Nitrous Oxide (N_2O)

It is an **oxide of nitrogen**, ***commonly known as*** **laughing gas**, **nitrous**, **nitro** or **NOS**.
- It is a ***non*-irritating *potent*** **analgesic** ***but*** a ***weak*** **general anesthetic**, if **used** ***alone*** *cannot* **produce surgical anesthesia**, ***but*** it is ***commonly combined*** with *other* ***more*** **potent anesthetic**.
It is ***used*** in **surgery** and **dentistry** for its **anaesthetic** and **analgesic effects**. It is known as **"laughing gas"** ***due to*** the **euphoric effects** of inhaling.
Nitrous oxide is ***poorly*** **soluble** in **blood** and **other tissues**, allowing it to ***move very*** **rapidly** **in** (***induction***) and **out** (***recovery***) of the ***body***.
- ***Concentrations***; in ***general anesthesia***, **30 %** to **70 %** in ***combination*** with **oxygen**.
Safety; **Nitrous oxide** ***does not depress*** **respiration** and ***does not produce*** **muscle relaxation**, ***little*** or ***no effect*** on **CVS** or **cerebral blood flow**, ***last*** **hepatotoxic** ***effect***.
- ***Side effects***; **Hallucination**, ***Postoperative*** **nausea** and **vomiting**.
- ***Prolonged*** **exposure** may cause **megaloblastic anemia**.

Halothane (Fluothane®)#

- **Halothane** is ***halogenated hydrocarbon***.
It is produce; ***rapid*** **induction**, ***quick*** **recovery**, ***not adequate*** **analgesia** (usually co-administered with **Nitrous oxide**, **opioids**, or **local anesthetics**) and ***not sufficient*** **muscle relaxation** (**neuromuscular backers** *may be required*, **dose** ***must be adjusted***, due to **Halothane** ***markedly augments*** the **non-depolarizing neuromuscular blocking effects**).
- ***Metabolism***; **oxidation** to **tissue-toxic hydrocarbons** (e.g. **Trifluoroethanol**) & **Bromide ion**.
Uses; ***induction*** and ***maintenance*** of **general anesthesia**.
Halothane and **Sevoflurane** ***agents of choice*** in ***patients with*** **airway problems** (***not have*** **pungent odour** to ***stimulate*** **respiratory reflexes**).
* **Hepatotoxicity** (**Halothane Hepatitis**); **Liver damage**, from ***mild*** **hepatitis** to **hepatic necrosis**.
* **Malignant Hyperthermia**; **Halothane** with **Succinylcholine** (***neuromuscular blocker***).
- ***Due to*** **side effects**; **Halothane** has been ***replaced*** in ***most*** **countries** by **newer agents** such as **Sevoflurane**, **Isoflurane** and **Desflurane**.

Isoflurane (Forane®)#

Isoflurane is a ***structural isomer*** of **Enflurane** (**Ethrane®**), **Enflurane** ***no*** **longer use** *due to* ***depression*** of **myocardial contractility**, ***higher*** **metabolism** (***high*** **toxic metabolites**, ***potentially*** **nephrotoxic**) and ***lower*** **seizures threshold**.
- ***Little*** **metabolism** (***less*** **toxic metabolites**), ***no*** or ***little*** **hepatotoxicity**.

N.B.; **Hepatic metabolism rank** for **inhaled anesthetics** is; **Halothane** > **Enflurane** > **Sevoflurane** > **Isoflurane** > **Desflurane** > **Nitrous oxide**.

Cardiac arrhythmias or ***dose-dependent*** **hypotension** ***may occur*** (*Other* ***newer*** **inhaled anesthetics** **Desflurane** and **Sevoflurane** are considerably ***less*** **arrhythmogenic**).
- It has a **pungent odour** and ***stimulates*** **respiratory reflexes** (breath holding, salivation, coughing and laryngospasm or bronchospasm), so ***not*** **used** in for **inhalation induction**.
- ***Used*** for ***maintenance*** of **general anesthesia**.
- ***Concern***; Use of **Isoflurane** and **Ketamine** in ***together*** in **infants** or **young children**, may ***increase*** **risk** of **neurodegeneration**.
- ***Now***; **Isoflurane** is ***being*** **replaced** ***with*** **Sevoflurane** and **Desflurane**.

Desflurane (Suprane®)#

- It is *very* **rapid onset** and **recovery** due to ***low* blood solubility**.

Like* Isoflurane**, it has a **pungent odour**, ***used for ***maintenance*** of **general anesthesia**, ***but*** due to ***high* cost** may ***precludes*** its **use**.

- ***Metabolism***; is ***minimal*** and **tissue toxicity** is ***rare***.

Sevoflurane (Sevorane®)#

- It has ***low* pungency**, ***used*** for ***induction*** and ***maintenance*** of **general anesthesia** in **adult *and* paediatric**.
- It has a ***rapid* onset** and **recovery** due to ***low* blood solubility**.
- ***Metabolism*** of **Sevoflurane** may ***generate* toxic metabolites** that are ***potentially* nephrotoxic**.
- ***N.B.***; - **Isoflurane**, **Desflurane** and **Sevoflurane** are a ***trigger*** of **malignant hyperthermia**.
  - **Mutagenicity**, **teratogenicity**, **reproductive effects** and **carcinogenicity** are a **chronic toxicity** for **inhalation anesthetics**, ***increase*** in **operating room personnel** who were exposed to trace concentrations of anesthetic agents.
  - **Methoxyflurane** is ***another* halogenated anesthetic** has ***not been* hepatotoxicity** *reported* after administration, *However*, **fluoride *release from* prolonged use** of **Methoxyflurane** has caused ***renal insufficiency***.

Intravenous Anesthetics

Barbiturates

Thiopental (Pentothal®) | **Methohexital** (Brevital®)

- ***This agents*** have been ***largely replaced*** as **induction anesthetics** by **Propofol**.
- It is a ***potent* anesthetic** <u>**but**</u> a ***weak* analgesic**.
- **Thiopental *induce* anesthesia *within* 30-60 seconds *after* IV injection**.
- ***All* barbiturates** are ***potent* cardiac** and **respiratory depressant**, *These agents* have been ***largely replaced*** as **induction anesthetics** by **Propofol**.

Benzodiazepines

Midazolam (Dormicum®)# | **Lorazepam** (Ativan®)#

Diazepam (Valium®)#

- **Benzodiazepines** (*still commonly used*); **Midazolam** (*short*), **Lorazepam** (*intermediate*) and **Diazepam** (*long*) are ***commonly*** used in **Preanesthetic medications** with **anesthetics**.
- Their ***most* desired effects** are **anxiolytic** and **providing amnesia**.
- ***All* benzodiazepines** are ***minimal* cardiac** and **respiratory depressant**.

Intravenous Anesthetics

Propofol (Diprivan®)#

Propofol is a ***short-acting* IV anesthetic** (***potent* anesthetic** but a ***weak* analgesic**) ***used for induction*** and ***maintenance*** of **anesthesia**.

It is ***widely* used** and has ***replaced* Thiopental** as the ***first choice*** for ***induction*** of **anesthesia**.

Formulation; ***Poor* solubility** in **water**, it is formulated as an **emulsion** (10% soybean oil, 2.25% glycerol and 1.2% lecithin{egg phospholipid}), it has been ***referred to*** as **milk of amnesia *because*** of the **milk-like appearance** (it is ***contraindicated*** in patients with allergies to **eggs** or **soy products**).

- ***Not used*** after **8 hours** of **vial opening** (*bacterial growth*).

- ***Pharmacokinetics***; - ***Onset***: **30-40 seconds** ***after administration***.
  - ***Duration***; **5-10 minutes**.
  - ***Metabolism***; ***Rapidly*** **metabolized** in the **liver**.
- ***Excretion***; ***inactive*** **water soluble metabolites** are **excreted** ***renally***.
- **Propofol** ***produces***;
  - ***Decrease*** **blood pressure**.
  - ***Minimal*** **respiratory depressant**.

Sub-anesthetic **doses** of **Propofol** can be ***used*** to ***treat*** **postoperative nausea** and **vomiting**.

- The **respiratory depressant** of **Propofol** are ***increased*** *if* **given** with ***other*** **respiratory depressants** (**benzodiazepines**), Michael Jackson was died of acute **Propofol** & **benzodiazepine** intoxication at home.

Fospropofol (**Lusedra**®) is a ***water-soluble prodrug*** of **Propofol**, ***approved*** in **2008** as a **sedating agent** for ***use*** during **Monitored Anesthesia Care** (**MAC**).

Etomidate (Amidate®)#

Etomidate is a ***short-acting*** **IV anesthetic**, ***used for induction*** of **anesthesia**.

- **Etomidate** ***not*** has **analgesic effects**.
- ***Formulation***; it is ***poorly*** **soluble** in **water** and is ***formulated in*** a **propylene glycol** ***solution***.
- ***Pharmacokinetics***; - ***Onset***; **30-60 seconds** ***after administration***.
  - ***Duration***; ***depends*** on **redistribution** to inactive tissue sites.
  - ***Metabolism***; *Primarily* by **ester hydrolysis**.
  - ***Excretion***; ***Inactive*** **metabolites** are excreted in **urine** (78%) & **bile** (22%)

It has ***little*** or ***no*** **effect** on the **heart** and **circulation**, it is **used** ***especially*** in **patients** ***with*** **cardiovascular dysfunction**.

- ***Side effects***; ***decrease*** **plasma cortisol** & **aldosterone** (*increased with prolonged infusion*).
- ***Combination*** of **Etomidate** with **opioids** and/or **benzodiazepines**, may exacerbate **Etomidate-*related*** **adrenal insufficiency**.

Ketamine (Ketalar®)#

It ***induces*** **dissociative anesthesia** (**trance-like state**); **analgesia-amnesia state** in which the **patient's eyes** ***remain*** **open**, but is ***dissociated from*** the **environment**, is **immobile** and ***does not respond*** to **pain**.

- ***Pharmacokinetics***; - ***Routes***; **IV**, **IM**, **oral**, & **topical routes**.
  - ***Onset***; **IV**; ***within*** a **minute**, **IM**; 5-15 min, **Oral**; 30 min.
  - ***Duration***; ***More*** **prolonged** (*depend on elimination*).
  - ***Metabolism***; In the **liver** by **CYP450 system**.
  - ***Excretion***; In urine.
- It ***has*** **effect** on the **heart** and **circulation** (***increase*** **blood pressure** and **CO**).
- It is ***not*** produce **respiratory depression**, and ***may*** cause **bronchodilation**, It ***increase*** **cerebrospinal fluid** ***pressure***.

It is ***beneficial*** in **patients** ***with*** **hypovolemic** or **cardiogenic shock** and **asthmatic**.

Side effects; **Psychic disturbances** (**unpleasant dreams**, **delirium** and **hallucinations**).

- **Ketamine** may be *used* **illicitly**, "**ecstasy drug**" it causes a ***dream-like*** **state** and **hallucinations**.

Dexmedetomidine (Precedex®)#

- It is an α_2 **receptor** *agonist*. It has **sedative**, **analgesic**, **sympatholytic** and **anxiolytic effects**.
- It is ***not*** produce **respiratory depression**, ***moderate decrease*** in **blood pressure** & **heart rate**.

Droperidol/Fentanyl (Innovar®)#

- **Droperidol** (antipsychotic) in ***combination*** with **Fentanyl** (opioid) usually provide **amnesia** and **analgesia**, and has been ***used*** to ***produce*** **neuroleptanalgesia** and **neuroleptanesthesia**.
- ***Side effects***; **Hypotension**, **QT interval** ***prolongation***, and **extrapyramidal syndrome**.

Local Anesthetics (LAs)

Esters

Cocaine

- It is the *first* used in **1884** and *strong* **stimulant** *mostly used* **illegal drug** *globally*.
- **Cocaine** *inhibits* **reuptake** of **serotonin**, **norepinephrine** and **dopamine**.
- **Cocaine** has since been *largely replaced* in **medicine** by *synthetic* **local anesthetics**.

Benzocaine

- **Benzocaine** is the *first* **synthetic** derivative of **Cocaine**, was developed in **1890**.

It is *found* in many **OTC anesthetic products** *used mainly* for **oral ulcers**.

The **topical use** of *higher concentration* of **Benzocaine** may *cause* **Methemoglobinemia**, this *side effect* is **most common** in **children** *under* **2 years**.

Procaine (Novocain®)#

- **Procaine** was *first synthesized* in **1905**. *To this day*, **Procaine** is *used less frequently*.

Procaine and *many* **other local anesthetics** are *used* *mainly* in *combination* with **Epinephrine** (*vasoconstrictor*), *to*; **1**) *Reduce* bleeding.
2) *Increases* duration and quality of anesthesia (decrease absorption).
3) *Decrease* amount of drug from reaching systemic circulation.

Tetracaine (Pontocaine®)#

It is *mainly* *used* *topically* in **ophthalmology** (topical local anesthetic for the eyes).

Chloroprocaine (Nesacaine®)#

Rapidly **metabolized** and *placental* **transfer** is *limited*, so, it is *used*, for **epidural anesthesia**.

Amides

Lidocaine (Xylocaine®)# (Lignocaine®)#

- **Lidocaine** *used* **systemic** as an **antiarrhythmic drug** (Class Ib) and **locally** as **local anesthetic**.

Like **Chloroprocaine**, *sometimes* *used* for **epidural anesthesia**.

Like **Tetracaine**, *can* be *used* *topically* in **ophthalmology**.

Inhaled **Lidocaine** can be *used* as an **antitussive** (*reduce cough reflex*).

- **Lidocaine** is *available* in *multiple* **formulations** and *most widely* **used**.

Mepivacaine (Mepecaine®)#

- **Mepivacaine** is a **local anesthetic** with *rapid* **onset** and *medium* **duration of action**.
- It *may* *used* for **epidural anesthesia** (*poor choice*).

Bupivacaine (Marcaine®)#

It is a **local anesthetic** *used* for **epidural anesthesia**, *but* it has *markedly* **cardiotoxic**.

- **Levobupivacaine** (**Chirocaine®**) is the *S-enantiomer* of **Bupivacaine**, *with less* **cardiotoxic**, *less* **potent** and *longer* **duration** than the racemic mixture.

Ropivacaine (Naropin®)#

- **Ropivacaine** was developed after **Bupivacaine**, was *with less* **cardiotoxic**.

It is also a *popular choice* for **nerve block anaesthesia** and **epidural anesthesia**.

Articaine (Septocaine®)

- It was *approved* as a **dental anesthetic** in 2000. Available in a *combination* with **Epinephrine**.
- **Articaine** is the *best choice* of **local anesthetic** in *modern* **dentistry**.
- *Characteristics* *over than* *other* **local anesthetics**; *low* **lipid solubility**, *high* **plasma protein binding**, *fast* **metabolization**, *fast* **elimination** and *low* **blood level**.

Prilocaine

- **Prilocaine** also *combined with* **Lidocaine** as a *topical* **preparation** for **dermal anesthesia**.

EMLA® (**E**utectic **M**ixture of **L**ocal **A**nesthetics); **Lidocaine** and **Prilocaine** are **solid bases**, when mixed in equal quantities, they form a **eutectic mixture**, that is the **melting point** of the **mixture** is *lower than* the **melting points** of the **individual components**.

Hormones

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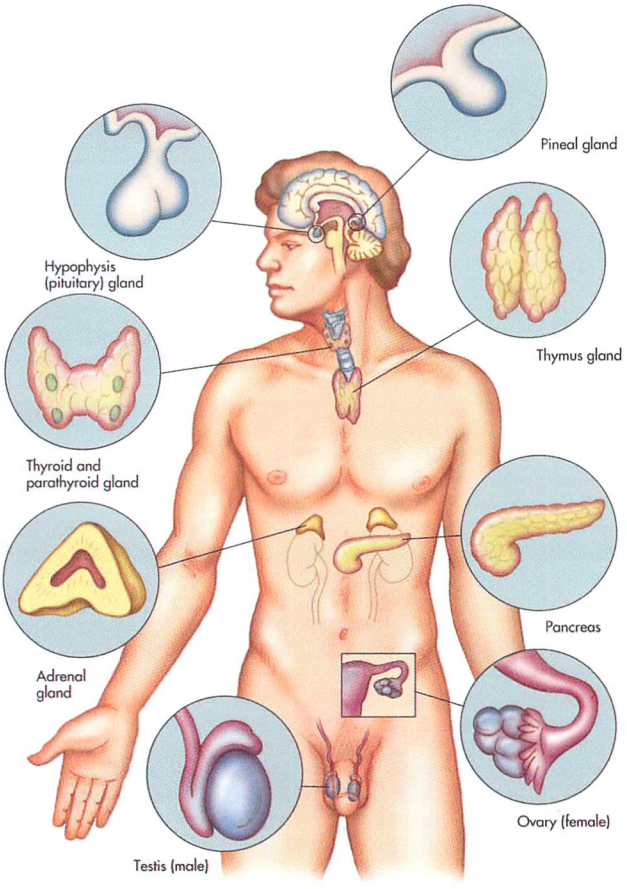
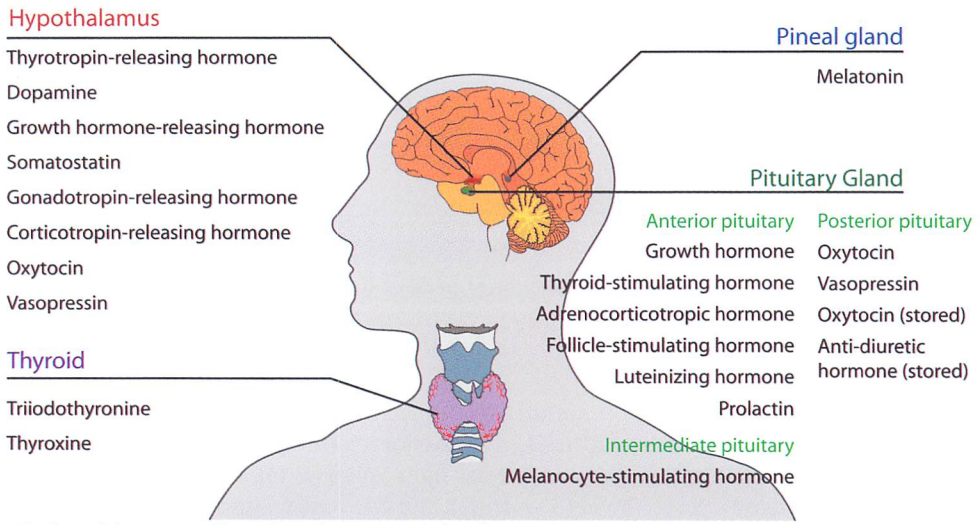
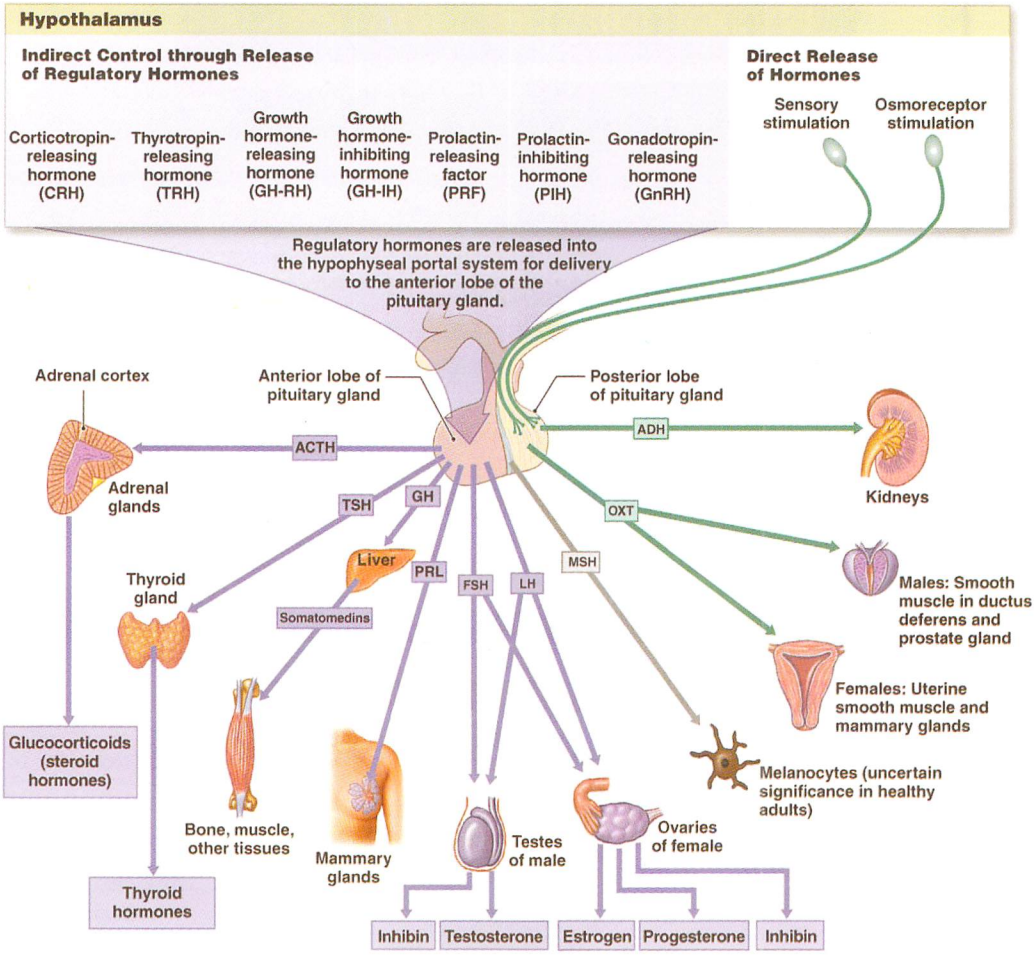


Hypothalamic Hormones

Thyrotropin-releasing Hormone (TRH)	- *Stimulate* Thyroid-stimulating Hormone (TSH) *release from* anterior pituitary.
Dopamine (Prolactin-inhibiting Hormone; PIH)	- *Inhibit* Prolactin (PRL) *release from* anterior pituitary.
Growth Hormone-releasing Hormone (GHRH)	- *Stimulate* Growth Hormone (GH) *release from* anterior pituitary.
Somatostatin (SS) (Growth Hormone-Inhibiting Hormone; GHIH)	- *Inhibit* Growth Hormone (GH) *release from* anterior pituitary.
Gonadotropin-releasing Hormone (GnRH)	- *Stimulates* Follicle-stimulating Hormone (FSH) and Luteinizing Hormone (LH) *release from* anterior pituitary.
Corticotropin-releasing Hormone (CRH)	- *Stimulates* Adrenocorticotropic Hormone (ACTH) *release from* anterior pituitary.
Oxytocin	- *Stimulates* uterine muscle contractions and release of milk by mammary glands (*stored* and *secreted* into bloodstream by posterior pituitary).
Vasopressin (Antidiuretic Hormone; ADH)	- Stimulates water reabsorption by kidneys (*stored* and *secreted* into bloodstream by posterior pituitary).



- **Pineal gland** is a ***small*** **endocrine gland** in the **brain**.
- The **pineal gland** ***produces*** **Melatonin hormone**, a **Serotonin** ***derived hormone*** which ***modulates*** **sleep patterns** in *both* **circadian** and **seasonal cycles**.
- **Melatonin Supplement** ***Uses***; **Circadian rhythm sleep disorders**, **Shift work disorder** and **Insomnia**.



Pituitary Hormones

Growth Hormone (GH)

IU × 0.333 = mg
mg × 3 = IU

Somatotropin Analogs

Somatropin (Humatrope®)# (Genotropin®)# (Norditropin®)# (Somatotropin®)#

A *recombinant form* of **GH** or **somatotropin**; called **Somatropin**.

- **Growth hormone** ↑ **protein synthesis**, **cell division** ⇨ *Increase* **number** and **size** of **cell** ⇨ ↑ *size* of **tissue** and **organs**; *growth of* **linear bone**, **skeletal muscle** and **organs**.

Uses; **GH Deficiency**, **Short-bowel Syndrome** and **HIV-associated Wasting** or **Cachexia**.

Off-label; **Performance enhancement in athletes** (2–7 IU usually 4 IU).

Dose; **0.2-0.3 mg/day** (0.6–0.9 IU) **SC** ***initially***.

Administration; **SC** or **IM**, but ***not all*** **products** are *approved for* **IM** *administration*.

Side effects; **Headache**, **nausea**, **vomiting**, **fatigue**, **muscle pain**, or **weakness**.

Precautions; ***Disease-related concerns***, **diabetes**, **pituitary gland disorder**, **hypothyroidism**, ***history of*** **head injury** or **brain tumor**, ***history of*** **childhood brain cancer**.

Mecasermin (Increlex®) | Mecasermin Rinfabate (Iplex®)

Mecasermin is a ***recombinant human*** **Insulin-like Growth Factor-1** (***rh*IGF-1**).

Mecasermin Rinfabate is a ***combination*** of ***rh*IGF-1** and **insulin-like growth factor binding protein-3** (**IGFBP-3**). **IGFBP-3** ***serves*** to ***prolong*** the **action** of **IGF-1**.

Uses; ***Long-term*** **treatment** of **growth failure** in ***children*** with ***severe*** **primary IGF-1 deficiency** (***Primary*** **IGFD**) or *with* **GH gene** ***deletion*** or **GH** ***insensitivity*** (Laron syndrome).

Most common Side Effects; **hypoglycemia** (carbohydrate-containing meal or snack 20 minutes before or after Mecasermin administration is recommended).

Somatostatin Analogs

Octreotide (Sandostatin®)#

Octreotide is a ***synthetic analogs*** of **Somatostatin** (Growth Hormone-Inhibiting Hormone; GHIH).

It is the ***most widely*** **used somatostatin analog**, is **45 times** ***more potent*** than **Somatostatin** in ***inhibiting*** **GH** ***release*** but **only** ***twice*** as **potent** in ***reducing*** **Insulin** ***secretion***.

Half-life; *about* **80 minutes** (**30 times** ***longer*** *than* that of **Somatostatin**).

Uses;

- **Acromegaly**.
- **Carcinoid Tumors** (inhibits severe diarrhea and flushing episodes).
- **Vasoactive Intestinal Peptide Tumors** (inhibits profuse watery diarrhea).

Off-label uses; - *Usually*; 50–200mcg SC every 8 hours
- Esophageal Variceal Bleeding; IV bolus *then* infusion.
- **Esophageal variceal bleeding**.
- **AIDS-Related Diarrhea**.
- **Chemotherapy-Related Diarrhea**.
- **Chylothorax**.
- **GI** or **Pancreatic Fistula**.
- **Ileostomy-Related Diarrhea**.
- **Dumping Syndrome**.
- **Neuroendocrine Tumors**.

- **Depot** ***formulations*** are **available** (**Sandostatin® LAR Depot**), allowing for ***administration*** **once** ***every*** **4 weeks**.

Vitamin B_{12} ***deficiency*** *may* **occur** with ***long-term*** **use** of **Octreotide**.

Side effects; - **Gallbladder** ***problems*** (reduction of bile production and gallbladder contractility, which leads to increased viscosity of bile and increased incidence of gallstones), **Dysglycemia** (hyper or hypo), **Hypothyroidism** and **Bradycardia**.
- **Nausea/vomiting**, **abdominal cramps** and **steatorrhea** *with* **bulky bowel movements**.

Lanreotide (Somatuline®)

Lanreotide is a ***synthetic analogs*** of **Somatostatin**.

Lanreotide ***reducing*** **GH** and ***normalizing*** **IGF-1** ***levels*** (**Octreotide** ↓ **GH** and **IGF-1** ***levels***)

Half-life; **23** to **30 days** (**Usually dose**; 90-120 mg SC *every* 4 Week).

Uses; **Acromegaly** and **Gastroenteropancreatic Neuroendocrine Tumors**.

- ***Side effects***; *Like* **Octreotide**.

Growth Hormone Receptor Antagonist

Pegvisomant (Somavert®)

Uses; **Acromegaly** in ***patients who*** have ***inadequate response*** to **surgery** or **radiation therapy**.

Dose;

- ***Initial***: 40 mg SC.
- ***Maintenance***: 10-30 mg by SC daily.

Prolactin Hormone (PRL)

Prolactin *responsible for* - ***Stimulate*** & ***maintain*** **milk** ***secretion***.
- ***Inhibit*** **ovulation** in **female**.

Hyperprolactinemia;
- *In* **female**; **Galactorrhea, amenorrhea**, and ***decrease*** **libido**.
- *In* **male**; **Gynecomastia, impotence, infertility** and ***decrease*** **libido**.

- **Dopamine** (**Prolactin-inhibiting hormone**) ⇨ ***Inhibit*** **Prolactin** ***release***.

Bromocriptine (Lactodel®)#

Bromocriptine (an ***ergot derivative***) is a **dopamine** ***agonist*** that is **used** in the ***treatment*** of **Parkinson's disease, Hyperprolactinaemia, Neuroleptic Malignant Syndrome** (**NMS**) and **Type 2 Diabetes**.

Dose ***for*** **Hyperprolactinaemia**;
- ***Initial***: **1.25 mg** to **2.5 mg orally** ***daily***.
- ***Titration***: ***Add*** **2.5 mg orally, as** ***tolerated***, to the **treatment dosage** ***every*** **2** to **7** ***days***.
- ***Maintenance***: **2.5 mg** to **15 mg orally** ***daily***.

- ***Side Effects***; - **Hallucinations, confusion, delirium, nausea** and **orthostatic hypotension**.
- ***Potential*** to cause **pulmonary** and **retroperitoneal** ***fibrosis***.

Used *with* ***caution*** in **patients** ***with*** **history** ***of*** **myocardial infarction** or **peripheral vascular disease**.

Cabergoline (Dostinex®)#

Cabergoline is a ***long-acting*** **dopamine agonist** with a ***high affinity*** for **D_2 receptors**.

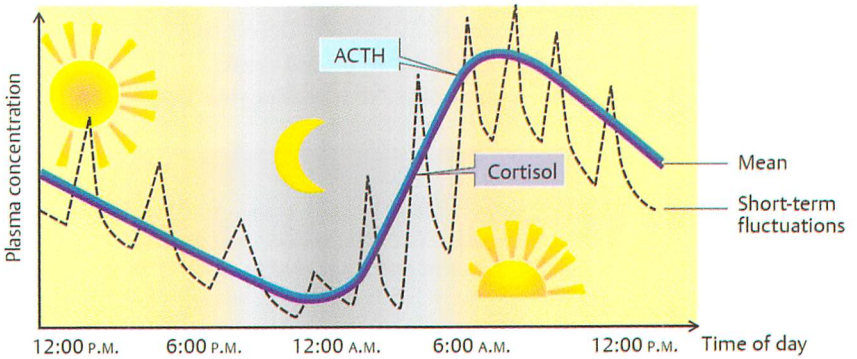
Uses; **Hyperprolactinaemia**.

Dose; - ***Prevent*** **lactation**; **1 mg (2 tablets)** on the **first day** ***after*** **delivery**.
- ***Stop*** **lactation** ***after*** **breast-feed**; **0.25 mg (1/2 tablet)** ***every*** **12 hours** *for* **two days**.
- ***Reduce*** **prolactin levels** in ***other*** **conditions**; **0.5 mg/week** ***spread out*** **over** a **week** (e.g. 1/2 tablet on Monday and the other 1/2 of the tablet on Thursday).

- ***Pregnancy***: **Category B**.
- ***Side effects***; **drowsiness, nausea, headache, dizziness, vertigo** and **GI disturbance**.

Adrenocorticotropic Hormone (ACTH)

- **Adrenocorticotropic hormone** (**ACTH**), also known as **Corticotropin**.
- **ACTH** ***stimulates*** **secretion of glucocorticoid** ***hormones*** from **adrenal cortex cells**.
- ***Plasma*** **ACTH** & **Cortisol** *levels* ***exhibit*** ↑ **peaks** (**6-8 AM**) & ↓ **nadirs** (**11 PM**).



Cosyntropin or Tetracosactide Acetate or Tetracosactide (Synacthen®)#

- **Cosyntropin** use as ***diagnostic agent*** in **adrenocortical insufficiency** (**ACTH stimulation test**); differentiating between primary adrenal insufficiency (Addison's disease which adrenal glands do not produce sufficient glucocorticoids and mineralocorticoids) and secondary adrenal insufficiency (caused by the inadequate secretion of ACTH by the pituitary); Primary adrenal insufficiency cannot be stimulated by ACTH where a secondary adrenal insufficiency will respond to adequate stimulation with ACTH.
- ***Dose***; 0.25 to 0.75 mg IM or IV over 2 minutes.
- **Cosyntropin** ***can*** be **used** in ***short-term*** **therapy** in ***conditions for*** which **Glucocorticoids** are ***usually*** **used** such as **rheumatic diseases**.

Repository Corticotropin Injection (HP Acthar® Gel)#

- **HP Acthar® Gel**; is a ***highly*** **purified** **Adrenocorticotropic hormone** (**ACTH**).
- ***Uses***; **Infantile spasms, multiple sclerosis, rheumatic disorder, inflammatory dermatologic diseases, inflammatory ophthalmic diseases, symptomatic sarcoidosis** and **edematous state**.

Thyroid-Stimulating Hormone (TSH)

- **Thyroid-Stimulating Hormone** (**TSH**); Also known as **Thyrotropin**.
- **TSH** ***stimulates*** the **thyroid gland** to ***produce*** **Thyroxine** (T_4) and **Triiodothyronine** (T_3); the ***effects*** of T_3 **3-4 times** ***more*** **potent** than T_4.

Thyrotropin alfa (Thyrogen®)

- ***Uses***; as **adjunctive diagnostic tool** for ***serum*** **Thyroglobulin** (**Tg**) ***testing*** *with* or *without* **radioiodine imaging** to ***differentiated*** **thyroid cancer**.
- **Thyroglobulin** (**Tg**) is a ***protein*** *produced by* the **thyroid**.
- **Tg** used by ***thyroid gland*** to *produce* the **thyroid hormones** T_4 & T_3.
- **Tg** ***levels*** in the **blood** can be used as a ***tumor marker*** for *certain kinds* of **thyroid cancer** because **Tg** is ***not*** *produced by* **medullary** or **anaplastic thyroid carcinoma**.

Gonadotropins

All **gonadotropin preparations** are ***pregnancy*** **category X** ***should be avoid*** *after* **pregnancy**.

	Luteinizing Hormone (LH)	Follicle-stimulating Hormone (FSH)
Female	- ***Induces*** **ovulation**. - ***Development*** of the **corpus luteum** to *produce* **Progesterone**.	- ***Stimulates*** the **growth** of ***immature*** **ovarian follicles** in the **ovary** *to produce* **Estrogen**.
Male	- ***Stimulate*** **Leydig cells (interstitial cells)** of the **testis** *to produce* **Testosterone**.	- ***Stimulate*** **spermatogenesis**. - ***Stimulates*** **Sertoli cells** to ***produce*** **androgen-binding protein** (**ABP**).

FSH Preparations

Urofollitropin (Fertinex®)# (Fostimon®)# (Metrodin®)#

Follitropin Alfa (Gonal-F®)# (Epigonal®)# | **Follitropin Beta** (Puregon®)#

Urofollitropin is a ***highly*** **purified** **FSH** ***extracted from*** the **urine** of **postmenopausal women**, while **Follitropin Alfa** and **Beta** are ***human*** **recombinant FSH** ***preparations***.

- **FSH** is ***required for*** *normal* **follicular growth, maturation, gonadal steroid production**, and **spermatogenesis**.

Uses; - **Assisted Reproductive Technology** (**ART**); such as **In Vitro Fertilization** (**IVF**).
- **Ovulation induction**: in women received **GnRH** ***agonist*** or ***antagonist*** for pituitary suppression.

- ***Dose***; **75-300 IU per day SC**.

Common Side Effects; **Headache** and **Ovarian Hyperstimulation Syndrome** (**OHSS**).

LH Preparations

Lutropin Alfa (Luveris®)

Lutropin alfa is the *first* and *only recombinant* form of *human* LH.

Uses; Follicle Stimulation; *Only* in *combination with* Follitropin *until* follicular *maturation* occurs in female infertility.

- *Dose*; 75-300 IU per day SC.

Common Side Effects; Headache and OHSS.

Other Preparations

Human Menopausal Gonadotropins (hMG) or Menotropin (Pergonal®)# (Menogon®)# (Merional®)# (Menopur®)#

Human Menopausal Gonadotropins (hMG) or Menotropins are *obtained from* the urine of menopausal women and *contains* FSH and LH.

Uses; - Assisted Reproductive Technology (ART); such as In Vitro Fertilization (IVF);
- Once adequate follicular development is evident, Human Chorionic Gonadotropins (hCG) should be administered one day following the last dose of Menotropins.
- *Infertility* in women and men.

- *Dose*; IM or SC 75-150 IU of FSH + 75-150 IU of LH *once* a day.

Common Side Effects; Headache, OHSS and multiple births.

Human Chorionic Gonadotropins (hCG) (Pregnyl®)# (Choriomon®)# (Epifasi®)#

Human Chorionic Gonadotropin (hCG) *produced by* human placenta and *excreted into* the urine.

- Choriogonadotropin alfa (rhCG) (Ovidrel®) is a *recombinant* form of hCG.

Uses; - Prepubertal cryptorchidism; *induce* testicular descent.
- Hypogonadotropic hypogonadism (*secondary to* a pituitary deficiency) in males.
- *Induction* of ovulation and pregnancy.

- *Dose*; IM *only* 500-1000 units *3 times* a week.

Common Side Effects; Ovarian cyst, OHSS, abdominal pain, nausea, vomiting and injection site inflammation.

GnRH and its Analogues

Gonadorelin (Factrel®)

Leuprolide (Lupron®)	Buserelin (Suprefact®)	Histrelin (Vantas®)
Goserelin (Zoladex®)#	Nafarelin (Synarel®)	Triptorelin (Decapeptyl®)#

- Gonadotropin-releasing hormone (GnRH) is a decapeptide (10 amino acids) *stimulates* the *synthesis* and *secretion* of the Gonadotropins, FSH and LH.

Gonadorelin is an *acetate* salt of *synthetic human* GnRH.

Leuprolide, Buserelin, Histrelin, Goserelin, Nafarelin & Triptorelin are GnRH analogues.
- They are effective in *suppressing* production of the Gonadotropins; *Initial* increase in FSH and LH *secretion* → *sustained* stimulation of GnRH receptors → hypogonadal effect (*decrease* FSH and LH); *due to down-regulation*. *Suppression* of Gonadotropins → *leads* to *reduced* production of gonadal steroid hormones (Androgens and Estrogens).

- *Pharmacokinetics*;
  - Gonadorelin *administered* IV or SC.
  - GnRH analogues can be *administered* SC, IM, nasal spray (Nafarelin & Buserelin) or SC implant.
  - *Durations of action*; from *several* hours (daily administration) to 1, 4, 6, or 12 months (depot forms).

Uses;
- **Gonadorelin**; ***Very short*** **half-life** (IV = 4 min);
  - ***Used*** as a **diagnostic agent** (assess pituitary gland function).
  - ***Unlike other*** **GnRH analogues**, it is ***not*** **used** to ***suppress*** **sex hormone** ***production***.
  - It is also ***used*** in the ***treatment*** of ***primary*** **hypothalamic amenorrhea, hypogonadotropic hypogonadism, delayed puberty, cryptorchidism & infertility**.
- **GnRH analogues**; ***More*** **potent** & ***long*** **lasting used** to ***suppress*** **sex hormone** ***production***.
  - ***Uses***; **Prostate cancer, breast cancer, endometriosis, uterine fibroids** and **early puberty**.
- **Triptorelin** (**Decapeptyl**®) is ***widely used*** in ***preparation for*** **In Vitro Fertilization (IVF)** ***undergoing controlled*** **ovarian hyperstimulation**;

Side Effects;
- **Gonadorelin**; **headache, light-headedness, nausea** and **flushing**.
- **Hypersensitivity dermatitis** and **local swelling** can occurs at ***SC injection***.
- **Sinusitis** can occur in ***nasal spray***.
- ***Within*** the ***first*** **month** of **therapy**; **Ovarian cysts** *may* **develop** due to its **flare effect** on **gonadotropin secretion** and generally ***resolve*** after an additional 6 weeks.
- ***Long term*** **use** causes **typical symptoms** of **menopause** (**hot flushes, sweats** and **headaches**), **depression**, ***diminished*** **libido**, ***generalized*** **pain, osteoporosis** and **vaginal dryness**.

GnRH Receptor Antagonists

Cetrorelix (Cetrotide®)#	**Ganirelix** (Orgalutran®)#
Abarelix (Plenaxis®)#	**Degarelix** (Firmagon®)#

- They are ***inhibit*** the ***secretion*** of **FSH** and **LH** in a ***dose-dependent*** **manner**.

Uses; - **Ganirelix** and **Cetrorelix** are ***approved for*** use in ***controlled*** **ovarian stimulation, In Vitro Fertilization (IVF)**; Inhibition of premature LH surges in women undergoing controlled ovarian stimulation.
- **Degarelix** and **Abarelix** are ***approved for*** men with ***advanced*** **prostate cancer**.

Common Side Effects;
- **Nausea** and **headache**.
- ***Long term*** **use** (**Degarelix** and **Abarelix**); **injection-site reactions, hot flashes, weight gain** and ***increases*** in **liver enzymes**.

Antidiuretic Hormone (ADH)

- **Antidiuretic Hormone** (**ADH**) or **Vasopressin**;
  - ***Stimulates*** **water retention**; ***Antidiuretic effect***.
  - ***Raises*** **blood pressure** by ***contracting*** **arterioles**; ***Vasopressor effect*** → **Vasopressin**.

Vasopressin and its Analogues

Vasopressin (Vasostrict®)	**Desmopressin** (DDAVP®) (Minirin®)#

- **Vasopressin injection** is a ***synthetic*** **Vasopressin hormone** for **IV, SC** or **IM** ***use***.
- **Desmopressin** or **1-Deamino-8-D-Arginine VasoPressin** (**DDAVP**®) is a ***long-acting*** **synthetic analog** of **Vasopressin** with ***minimal*** **pressor activity** and an **antidiuretic-*to*-pressor** ***ratio*** **4000** ***times*** that of **Vasopressin**.
- ***Administration***; - **Vasopressin**; **IV, SC** or **IM**.
  - **Desmopressin**; **IV, SC, intranasally** or **orally** (***Regular*** or ***melt*** **tablets**).
    - **Nasal administration** of **Desmopressin** may be ***less effective*** when **nasal congestion** is ***present***.

Uses;
Desmopressin (DDAVP®) (Minirin®);
- Diabetes Insipidus.
- Hemophilia A and von Willebrand disease (Type I).
- Bedwetting (Nocturnal Enuresis) and Nighttime Urination.

Minirin®; Regular tablets; 0.2 mg one hour before bedtime, if needed after 10 to 14 days, the dose may be increased by 0.2 mg to a maximum dose of 0.6 mg.

Minirin®-melt; Oral melt tablets; 120 µg sublingual are given 30 to 60 minutes before bedtime; if needed after 10 to 14 days, the dose may be increased by 120 µg to a maximum dose of 360 µg.

Vasopressin (Vasostrict®);
- IM/SC; Diabetes Insipidus, Abdominal Distention & Abdominal Roentgenography
- IV *infusion*; Esophageal variceal bleeding and colonic diverticular bleeding.
- IV *bolus*; in pulseless arrest (In *replacement* of Epinephrine in the Advanced Cardiovascular Life Support; ACLS *resuscitation* protocol).

- *Side effects*; - Headache, nausea, abdominal cramps and agitation.
- *Overdosage* can result in hyponatremia and seizures.

Vasopressin Receptor Antagonists

Conivaptan (Vaprisol®)	Tolvaptan (Samsca®)

- Conivaptan and Tolvaptan are *approved* by the FDA for *treatment* for hyponatremia *associated with* CHF, cirrhosis and SIADH.
- *Other* Vasopressin Receptor Antagonists *under development*; Mozavaptan (approved in Japan), Relcovaptan, Nelivaptan, Lixivaptan and Satavaptan.

Oxytocin

The word oxytocin was *derived from* Greek "oxys" and "tokos" *meaning* "quick birth".
Function;
- During labour; *Contraction* of the uterus to *facilitate* delivery.
- During lactation (*Suckling*); Contraction of myoepithelial cells *surrounding* mammary alveoli, which *leads to* milk ejection.
- Others; Oxytocin or Love Hormone is now *believed* to be involved in a *wide variety* of physiological and pathological functions *such as* sexual activity, orgasm, and ejaculation, maternal behavior, social bonding, stress and *probably many more*.

Oxytocin (Syntocinon®)#

- Oxytocin injection is a *synthetic* Oxytocin hormone for IV *infusion* or IM *use*.

Uses; - Labor Induction.
- Postpartum Hemorrhage.
- *Adjunctive therapy* in the management of *incomplete* or *inevitable* abortion.

- Oxytocin nasal spray *uses* (Off-label); *Promote* Lactation, Autism, *Delayed* Orgasm and Intensifying Sexual Arousal.

WARNINIG; *Excessive* stimulation of uterine contractions *before* delivery can *cause fetal* distress, placental *abruption*, or uterine *rupture*; Oxytocin injection in Labor Induction is *administered* ONLY by the IV *infusion* and with *adequate* medical supervision in a hospital.

Toxicity; - *High* concentrations of Oxytocin can *activate* of Vasopressin receptors can cause *excessive* fluid retention *leading* to hyponatremia, heart failure, seizures & death
- Bolus *injections* of Oxytocin can cause hypotension.

- Contraindications; Fetal distress, fetal malpresentation, placental abruption, and *other predispositions* for uterine rupture, *including previous* extensive uterine surgery.

Oxytocin Analogues

Carbetocin (Pabal®)	**Demoxytocin** (Sandopart®)

- **Carbetocin** and **Demoxytocin** are **Oxytocin** ***analogues*** with ***longer*** **half-life**.
- They are ***not*** **approved** by **US FDA**, but ***approved*** in ***some*** **countries** for ***used*** to ***induce*** **labor**, ***promote*** **lactation**, and **postpartum hemorrhage**.

Oxytocin Antagonist

Atosiban (Tractocile®)

- **Atosiban** is an **Oxytocin** ***receptor antagonist*** that has been ***approved outside*** the **United States** as a **treatment** (**tocolysis**) for **preterm labor** (**tocolytic agent**).
- **Atosiban** is ***useful*** in ***improving*** the **pregnancy outcome** of **In Vitro Fertilization-Embryo Transfer** (**IVF-ET**) in **patients** with ***Repeated*** **Implantation Failure** (**RIF**).

Thyroid and Antithyroid Drugs

Effects of Thyroid hormones

Effect on Cell Metabolism	**Mitochondria**	- ↑ **size** and **number** of **mitochondria** → ***leading to*** → ↑ **ATP formation**.
	Cell membrane	- ↑ ***activity*** of Na^+/K^+ **ATPase enzyme** → ↑ Na^+ and K^+ ***transport*** → ***energy*** **consumption** and **heat** ***production***.
Effect on Body Metabolism (Stimulate Basal Metabolic Rate; BMR)	**Carbohydrate**	- ***Stimulate all*** **carbohydrate** ***metabolism***: - ↑ **Insulin secretion** and **Glucose uptake by the cell**. - ↑ **Glycolysis** and **Gluconeogenesis**.
	Fat	- ***Increase*** **fat breakdown** (**lipolysis**) & ***decrease*** **fat store**.
	Protein	- ***Stimulate both*** **protein** ***synthesis*** and ***degradation***.
	Plasma lipids	- ***Increase*** **free fatty acids** ***levels***. - ***Decrease*** **cholesterol**, **triglyceride** and **phospholipids**; - ***Increased*** **risk** of **coronary artery disease** in **hypothyroid patient**.
Effect on Growth		- **Mental development**; ***Importance*** in **fetal** for ***normal*** **mental development**; **fetal** ***without*** **thyroid** will ***remain*** **mentally deficient** *throughout* **life**; **Thyroid hormones test** ***should be*** **done** ***during*** **first day** of **fetal life**). - **Bone growth**; ***Important*** for ***normal*** **growth** and **fusion** of **bone**. - **Sexual maturation**; ***Important*** for **sexual maturation**.
Effect on Body System		- **CVS**; - **Calorigenic effect**; ↑ O_2 **consumption** & **heat production** - **Vasodilatation** in ***most*** **body tissues**; ↑ **blood flow**; - ***Supersensitivity*** of **sympathetic nervous system**. - ***Increase*** **cardiac output** and **heart rate** (**tachycardia**). - ***Increase*** **respiration**. - **CNS**; - **Mental development**. - ***Excitatory*** **effect** on **CNS**. - ***Too little*** **thyroid hormone** can *cause* **mentally sluggish**. - ***Too much*** **thyroid hormone** can *cause* **anxiety** and **nervousness**. - **GIT**; ***Increase*** **GI Motility** (***increase*** **appetite** and **food intake**); - **Hyperthyroidism** can cause **diarrhea** - **Hypothyroidism** can cause **constipation**.

Thyroid Drugs

Levothyroxine (Eltroxin®)# (Euthyrox®)# | **Liothyronine** (Cytomel®)

Levothyroxine or **L-thyroxine**, is a ***synthetic*** **form** of **Thyroxine** (T_4).
Liothyronine is a ***synthetic*** **form** of **Triiodothyronine** (T_3).
Liotrix (**Thyrolar**®) is a **4:1** ***mixture*** of T_4 and T_3 *made* ***synthetically***.
- **Tiratricol** (*also known as* **TRIAC** or **Triiodothyroacetic acid**) is a **thyroid hormone** ***analogue***, **used** as a **dietary supplement** for **thyroid problems** it is also **used** for ***increasing*** **metabolic rate** for **weight loss** and ***reducing*** **cellulite**; US FDA warnings to use of dietary supplements containing **Tiratricol**.

Pharmacokinetics;
- ***Absorption***; ***Both*** T_4 and T_3 are **absorbed** ***after*** **oral administration**.
  # # **Oral bioavailability**; T_4; **70-80%**. T_3; ***completely*** **absorbed (95%)**.
  # # **Food**, **Calcium** ***preparations*** and **Aluminum-*containing*** **antacids** can ***decrease*** the **absorption** of T_4 (**Fatty meal** and **coffee** ***lowers*** its **absorption**); **Thyroid hormones** ***must be*** **taken** in the **fasting state** (30-60 minutes before breakfast).
- ***Distribution***;
  # ***More than*** **99%** of ***circulating*** **thyroid hormones** are ***bound*** to **plasma proteins**; ***primary*** *to* **Thyroxine-binding Globulin** (**TBG**) and ***some*** *to* **Thyroxine-binding Prealbumin** (**TBPA**); T_4 has ***higher affinity*** than T_3.
- ***Metabolism***;
  1) **Sequential Deiodination** (major route of metabolism); ***About*** **80%** of ***circulating*** T_3 ***obtained from*** T_4 **deiodination** ***mainly*** in the **liver** & **kidneys**; **Amiodarone**, **Propranolol** & **Corticosteroids** → **inhibits** ***conversion*** of T_4 to T_3.
  2) **Conjugation** ***with*** **Glucuronides** and **Sulfates**; ***excreted*** in **feces**.
  3) **Deamination** and **Decarboxylation** ***excreted*** in **urine**.
- ***Elimination***; **Urine** (major) and **feces** (20%).

	Thyroxin (T_4)	Triiodothyronine (T_3)
Origin	Thyroid (100%)	- Thyroid (20%) - Deiodination of T_4 (80%)
Potency	1	4
Oral bioavailability	70-80%	95%
Half life	7 days	1 day
Protein binding form	99.96%	99.6%
Free form	0.04%	0.4%
Total serum level	5–11 mcg/dL	0.1–0.2 mcg/dL

Therapeutic Uses; *Treatment of* **Hypothyroidism**.
  # # **Levothyroxine** (T_4) is ***preferred over*** **Liothyronine** (T_3) or T_3/T_4 ***combination***; it is ***better*** **tolerated** and has a ***longer*** **half-life** (**Levothyroxine** is the ***drug*** of ***choice in*** **Hypothyroidism**).
  # # **Levothyroxine** is ***dosed*** **once daily**, and **steady state** is ***achieved*** in **6-8 weeks** (Monitoring of the patient's condition and adjustment of the dosage are necessary).
FDA Warning; **Thyroid hormones**, *either* ***alone*** or ***with*** *other* **therapeutic agents**, ***should*** **NOT** be used for the ***treatment of*** **obesity** or for **weight loss**.
Toxicity (***symptoms*** of **hyperthyroidism**); *such as* **Nervousness**, **palpitations**, **tachycardia**, **heat intolerance**, and ***unexplained*** **weight loss**.

Common Drug Interactions;
- **Heparin** and **oral anticoagulant** (↑ effect of anticoagulant).
- **Cholestyramine** (↓ absorption of ***Levothyroxine***).
- **Iron**, **calcium supplement**, **antacids** (↓ absorption of **Levothyroxine**).
- **Sucralfate** (↓ absorption of **Levothyroxine**).

Antithyroid Agents

Thioamides (Thyroid Peroxidase Inhibitors)

Propylthiouracil (PTU) (Thyrocil®) | **Methimazole** (Tapazole®)

Carbimazole (Neo-mercazole®)#

- **Propylthiouracil** (**PTU**) and **Methimazole**are ***major drugs*** for **treatment** of **Thyrotoxicosis**.
- **Carbimazole** is a ***pro-drug*** of **Methimazole** that is **used** ***only*** in **Europe**, **Australia** and ***other*** **countries** (not USA).
- **Methimazole** is about **10 times** ***more potent*** than **Propylthiouracil** and is the ***drug of choice*** in **adults** and **children** (*due to* **Propylthiouracil** has ***high*** **risk** of **hepatotoxicity**).
- ***Major Mechanism***; ***Inhibit*** **thyroid peroxidase enzyme** and ***blocking*** **iodine organification** → ***prevent*** **hormone synthesis**.
- ***Onset of action*** **these agents** is ***slow***, *often* ***requiring*** **3–4 weeks** ***before*** **stores** of T_4 are ***depleted***.
- ***Pregnancy***;
  - **Propylthiouracil** and **Methimazole** are ***classified as*** **FDA pregnancy category D** (***risk*** of **fetal hypothyroidism**); ***Caution*** **must** be ***employed*** when ***using*** these **drugs** in **pregnancy**.
  - **Propylthiouracil** is ***preferable during*** the **first trimester** of **pregnancy** because it is ***more strongly*** **protein-bound** and therefore, ***crosses*** the **placenta** ***less*** **readily** (**Methimazole** *may* **use** in **2nd** and **3rd** **trimesters**).
  - **Propylthiouracil** and **Methimazole** are ***secreted*** in ***low*** **concentrations** in **breast milk** *but* are **considered** ***safe*** for the **nursing infant**.
- ***Side Effects***;
  - **Skin** (***Most common*** **side effects**); **Dermatologic reactions** *with* **fever**.
  - **GIT** (Occur early); **Nausea** and **GI distress**.
  - **Liver**; - **Severe hepatitis** *with* **Propylthiouracil** (**black box warning**).
    - **Cholestatic jaundice** (*commonly with* **Methimazole**).
  - **Blood** (***Dangerous*** **complication**; ***rarely*** but **fatal**); **Agranulocytosis**.

Anion Inhibitors (Sodium-iodide Symporter Inhibitors)

Potassium Perchlorate (Perchloracap®)

- **Potassium perchlorate** is ***rarely*** **used** (*associated with* **aplastic anemia**).
- It ***block*** **thyroidal reuptake** of I^- in *patients with* **Iodide-*induced*** **Hyperthyroidism** such as **Amiodarone-*induced*** **Hyperthyroidism**.

Iodide Therapy (Blockade of Hormone Release)

Lugol's Iodine | **Potassium Iodide**

- **Lugol's iodine** is a ***solution*** of **Potassium Iodide** ***with*** **Iodine** in **water**; *used as* **Disinfectant** and for **Thyrotoxicosis** and as **preoperative preparation** for **surgery** (***decrease*** the **vascularity**, **size**, and **fragility** of a **hyperplastic gland**); ***not useful*** for **long-term therapy**.

Radioactive Iodine (RAI) - Iodine-131 (^{131}I)

- ^{131}I is the ***only*** **isotope** ***used*** *for* ***treatment*** of **Thyrotoxicosis** and ***some types*** of **thyroid cancer** that ***absorb*** **Iodine**.

Others

- **Ipodate** and **Iopanoic acid** are **Iodine-*containing*** **radiocontrast medium**, they are ***inhibit*** **peripheral conversion** of T_4 to T_3 and ↓ T_4 ***synthesis*** **used** ***off-label*** in **hyperthyroidism**.
- **β-blockers** *such as* **Propranolol**, are ***effective*** to ***control*** **sympathetic** ***stimulation*** that **occurs** in **hyperthyroidism** (it also ↓ T_3 levels by ***inhibiting*** the **peripheral conversion** of T_4 to T_3).

Adrenocortical Hormones

- **Adrenal Cortex** is ***formed*** by **3 layers**;
  1) **Zona Glomerulosa** (**Outer layer**); *about* **15%** of the **cortex**;
     - ***Producing*** **Mineralocorticoids**; **Aldosterone**.
  2) **Zona Fasciculata** (**Middle layer**); *about* **75%** of the **cortex**;
     - ***Producing*** **Glucocorticoids**; such as **Cortisol**.
  3) **Zona Reticularis** (**Inner layer**); *about* **10%** of the **cortex**;
     - ***Producing*** ***Adrenal*** **Androgens** such as **Dehydroepiandrosterone** (**DHEA**), **DHEA sulfate** and **Androstenedione** (*precursor* to **Testosterone**).

Mineralocorticoids

- **Mineralocorticoids** are a ***class of*** **steroid hormones** *characterized by* their ***influence on*** **salt** and **water** ***balances***.
- The ***name*** **Mineralocorticoid** *derives from* early *observations* that these **hormones** were ***involved in*** the ***retention*** of **Sodium**, a **mineral**.

The ***primary*** **mineralocorticoid** is **Aldosterone**.

Other ***endogenous*** **hormones** such as **Progesterone** and **Deoxycorticosterone** have **mineralocorticoid** ***function***.

Aldosterone ***secretion*** is *mediated* ***primary*** by **Angiotensin II** ***but*** also by **Adrenocorticotrophic Hormone** (**ACTH**) and ***local*** **Potassium** ***levels***.

Function; ***Reabsorption*** of **Na^+**, **water** and **Cl^-** and ***Excretion*** of **K^+** and **H^+**.

Synthetic Mineralocorticoids

Fludrocortisone (Astonin-H®)#

Fludrocortisone (**9α-fluorocortisol** or **9α-fluorohydrocortisone**) is a ***synthetic potent*** **mineralocorticoid** (250 parts salt-retaining) with ***some*** **glucocorticoid** ***activity*** (10 parts anti-inflammatory). **Fludrocortisone** is the ***most widely*** used **mineralocorticoid**.

Fludrocortisone Acetate is ***used*** **orally** to ***treat*** **Adrenocortical Insufficiency/Addison's Disease**, **Congenital Adrenal Hyperplasia** and **Postural Hypotension** (*off-label*).

- **Fludrocortisone** is also **used** in ***confirmation test*** for **diagnosing Conn's syndrome**.
- ***Usual Dose***; **0.1 mg/day** ***orally***.
- ***Side effects***; **Hypertension**, **edema**, **heart failure** and **hypokalemia**.

Mineralocorticoids Antagonists

Spironolactone (Aldactone®)#	**Eplerenone** (Inspra®)

Spironolactone is a ***synthetic*** **steroid** that *acts as* a **competitive antagonist** to **Aldosterone** at **mineralocorticoid receptors**. **Eplerenone** is a **Spironolactone** ***analogue*** with much ***greater*** **selectivity** for the **mineralocorticoid receptors**.

- **Eplerenone** has a ***several*** **hundredfold** ***less active*** on **androgen** and **progesterone receptors** than **Spironolactone**, therefore, **Eplerenone** has considerably ***fewer*** **side effects**.

Spironolactone ***uses***; **Primary hyperaldosteronism** (**Conn's syndrome**), **Edema**, **Essential hypertension**, **Hypokalemia** and **Antiandrogen** (**hirsutism**, **acne** in ***women*** & **androgenic alopecia**).

Eplerenone ***uses***; **Congestive heart failure post-myocardial infarction** and **Hypertension**.

Side effects; **hyperkalemia**, **metabolic acidosis** and **endocrine abnormalities** (*with* **Spironolactone**; **gynecomastia**, **impotence** and **menstrual irregularities**).

Glucocorticoids

- The *name* **Glucocorticoid** (**gluco**se + **cort**ex + ster**oid**) is *composed from* its **role** in *regulation* of **Glucose** *metabolism*, *synthesis* in the **adrenal cortex** and its **steroidal** *structure*.
- **Glucocorticoids** are **essential** *for* **life**; they are *regulates* or *supports* a *variety* of *important* **cardiovascular**, **metabolic**, **immunologic** and **homeostatic** *functions*.

Short Acting (<12 hours)	
Cortisol (**Hydrocortisone**) (Solu-Cortef®)#	**Cortisone** (Cortone Acetate®)#
Intermediate Acting (12-36 hours)	
Prednisone (Hostacortin®)#	**Prednisolone** (Hostacortin-H®)#
Triamcinolone (Kenacort-A®)#	**Methylprednisolone** (Solu-Medrol®)#
Long Acting (>48 hours)	
Betamethasone (Diprofos®)#	**Dexamethasone** (Dexamethasone®)#

Cortisol or **Hydrocortisone** and **Cortisone** are ***naturally*** *occurring* **Glucocorticoids**.
Prednisone is a ***prodrug*** that ***converted to*** **Prednisolone**, the **active compound** in the **liver**.
Hypothalamic-pituitary-adrenal axis, **circadian rhythm**, **stress** and ***low blood*** **glucose** ***level*** are the ***most important*** **factors** in **glucocorticoids** ***secretion*** **regulation**.
  # ***Plasma*** **ACTH** & **Cortisol** ***levels*** *exhibit* ↑ **peaks** (**6-8 AM**) & ↓ **nadirs** (**11 PM**).
Approximately **90%** of **Cortisol** is ***bound*** to **Cortisol-binding Globulin** (**CBG**), *while* **5–10%** is ***bound*** to **Albumin**; ***only*** **5%** of ***circulating*** **Cortisol** is **free** to ***exert*** its **effect** on **target cells**.
- **Brief** ***comparison*** *between* **Glucocorticoids** and **Mineralocorticoids**;

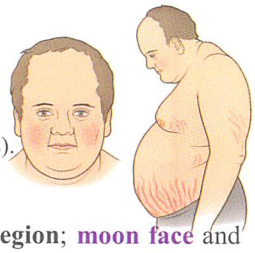
Agent	Activity			Equivalent Oral Dose (mg)	Forms Available
	Anti-Inflammatory	Topical	Salt-Retaining		
Cortisol	1	1	1	20	Oral, injectable, topical
Cortisone	0.8	0	0.8	25	Oral
Prednisone	4	0	0.3	5	Oral
Prednisolone	5	4	0.3	5	Oral, injectable
Methylprednisolone	5	5	0.25	4	Oral, injectable
Triamcinolone	5	5*	0	4	Oral, injectable, topical
Betamethasone	25-40	10	0	0.6	Oral, injectable, topical
Dexamethasone	30	10	0	0.75	Oral, injectable, topical
Fludrocortisone	10	0	250	2	Oral
Desoxycorticosterone	0	0	20		Injectable, pellets

* **Triamcinolone Acetonide**: ***Up to*** **100**

Table from; Basic and Clinical Pharmacology 14th edition, Katzung-Lange

Action of Glucocorticoids

1) ***Effect on metabolism***;
  A) **Carbohydrates Metabolism** (**Hyperglycemic** and **Diabetogenic**) [**Steroid Diabetes**];
    # ***Stimulate*** **gluconeogenesis** in the **liver**;
      - ↑ **amino acids** ***uptake*** by the **hepatic cell**.
      - ↑ ***activity*** of **enzyme** that ***convert*** **amino acid** *to* **glucose**.
    # ***Decrease*** **insulin sensitivity** of **muscle** and **adipose tissue** (**Anti-insulin**);
      - ↓ ***affinity*** of **insulin receptor** to **insulin**.
      - ↓ **glucose** ***transports*** from the **cell membrane** to ***inside*** the **cell**.
    # ***Resistance*** to **stress** → ↑ ***serum*** **glucose levels** to ***maintenance*** of an ***adequate*** **glucose** ***supply*** to the **brain**.



B) **Protein Metabolism**: (**Catabolic effect**);
- # ↓ **protein** ***synthesis*** & ↑ **protein** ***catabolism***.
- # ↑ **plasma amino acid** ***level***.
- # ↓ **amino acid** ***transport*** *into* **extrahepatic tissues**.
- # ↑ ***conversion*** of **amino acids** *into* **urea** (↑ ***breakdown*** of **amino acids**).

C) **Fat Metabolism** (**Lipolytic** and **Ketogenic**);
- # ↑ **lipolysis** → ↑ **Free Fatty Acids (FFA)** in the **blood**.
- # # # ***Redistribution*** of **fat** ***depot*** in the **facio-cervical-trunk region**; **moon face** and **buffalo hump** and in the **abdomen** → **purple striae** (*stretch marks*).

2) ***Effect on muscle***;
- # **Catabolic** ***effects*** → **weakness** and **muscle atrophy** (↓ protein synthesis).

3) ***Effect on CVS***; (**Hypertension**);
- # **+ve inotropic** ***effect*** (stimulation Na^+/K^+ ATPase and of β-adrenergic receptors).
- # **Na^+ & water** ***retention*** (↑ blood volume); weak mineralocorticoid effect.
- # ***Potentiate*** **vasoconstrictor effect** of **Norepinephrine** and **Angiotensin II**.

4) ***Effect on blood cells***;
- # ↓ **Lymphocytes**, **Monocytes**, **Basophils** and **Eosinophils**.
- # ↑ **Neutrophils**, **Platelets** and **RBCs**.

5) ***Effect on Kidney***;
- # ↑ **Glomerular Filtration Rate (GFR)**.
- # ↑ ***reabsorption*** of **Water**, **Sodium**, **Chloride**.
- # ↑ ***excretion*** of **Potassium**, **Calcium** and **Uric Acid**.
- # ↑ ***excretion*** of **H^+** → ↑ ***excretion*** of **NH_4^+** (↑ **ammoniagenesis**; **$H^+ + NH_3$**).

6) ***Effect on bone***; [**Osteoporosis**]
- # ↓ ***absorption*** of **Calcium** & **Phosphate** from ***intestine*** (**Anti-vitamin D**).
- # ↓ **bone** ***formation***; ↓ **osteoblast** ***number*** and their ***function***.
- # ↑ **bone** ***resorption***; ↑ **osteoclast** ***survival*** and ***activity***.

7) ***Effect on Skin***;
- # # # **Daily use** of **topical glucocorticoids** for ***several*** **weeks** [**Skin Atrophy** or **Steroid Atrophy** and **Skin Thinning**]; ↓ **collagen** ***synthesis*** by ↓ ***proliferation*** of **fibroblasts** → **thinning of skin** and ***easy*** **rupture**.
- # # # **Daily use** of **topical glucocorticoids** for ***several*** **months** or **years** [**Topical Steroid Addiction**; **TSA**]; *When* **topical glucocorticoids** is ***stopped*** → **skin redness**, **burning**, **itching**, **hot skin** and **swelling** (**Red Skin Syndrome** or **Topical Steroid Withdrawal**; **TSW**).

8) ***Effect on GIT*** [**Steroid Ulcers**];
- # **Ulcerogenic** ***effect***; - ↑ **gastric-acid** ***secretion***.
- # ↓ ***local*** **immune** ***response*** **against** ***H. pylori***.

9) ***Effect on Fetal lung***; [**Fetal Lung Maturation**]
- # ↑ ***production*** of **surfactants** (***necessary*** for ***extra*** **uterine lung function**).
- # **SURVANTA®** (**Beractant**); **pulmonary surfactants** ***intratracheal injection***; used for **Respiratory Distress Syndrome** (**RDS**) (hyaline membrane disease) in ***premature*** **infants**.

10) ***Effect on CNS***;
- # **Euphoria** and **behavioural** ***changes***.
- # ***Maintenance*** of **alpha rhythm** in **electroencephalogram** (**EEG**).
- # ↓ **seizure** ***threshold***.
- # ↑ ***intracranial*** **pressure** (**pseudotumor cerebri**).

11) ***Effect on Eye***;

Glaucoma (*due to* ***increased*** **ocular pressure**);

Cataracts.

12) ***Anti-inflammatory effect***;

Suppress **Phospholipase A_2** ***activity*** (↓ arachidonic acid synthesis → ↓ prostaglandins and leukotrienes synthesis).

Suppress **Cyclooxygenase (COX)** ***activity*** (↓ prostaglandins synthesis).

Suppress **proinflammatory cytokines**, and ***other*** **inflammatory mediators** ***release***; such as tumor necrosis factor-α (TNF-α) and interleukins.

Suppress **leukocytes** and **macrophages** ***migration***.

Stabilizing **mast cell** and **basophil** ***membranes*** → ↓ **Histamine** ***release***.

Decrease **capillary permeability** → ↓ ***inflammatory*** **edema**.

13) ***Anti-allergic effect***;

Decrease **antibody** ***formation***.

Decrease **antibody/antigen** ***reactions***.

Decrease **tissue response** to **allergic** ***mediators***.

Mast cell and **basophil** ***stabilization*** → ↓ **Histamine** ***release***.

14) ***Immunosuppressant effect***;

Inhibit **functions** of **Macrophages** and *other* **antigen-presenting cells**;

- Inhibits production of Interleukin-12, Interferon-γ and Tumor Necrosis Factor-α (TNF-α) by antigen-presenting cells (dendritic cells, macrophages and B-lymphocytes) and T helper-1 cells.

Prevents **T-cells proliferation**;

- Decrease T-cells response to Interleukin-1 → T-cells unable to produce Interleukin-2.

15) ***Anti-shock Effect***;

Unfavourable **stress**; such as **acute trauma**, **major surgery**, **severe infection** or **emotional stress**; ↑ **CRH** → ↑ **ACTH** → ↑ **Cortisol**;

- **Hypervolemia** and **Hyperglycemia** ***effects***.
- ***Potentiate*** **sympathetic action**.

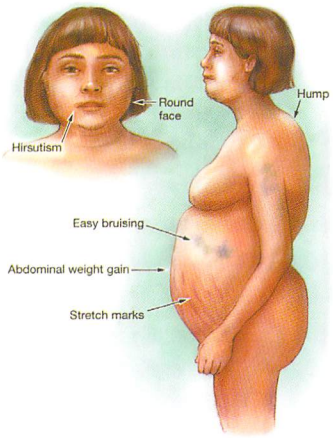
16) ***Withdrawal***;

Glucocorticoids ***cannot*** *be* ***stopped*** **abruptly** and ***must*** *be* ***stopped*** **gradually** to ***avoid*** **Cortisol** ***deficiency*** *resulting from* **hypothalamic-pituitary-adrenal axis (HPA)** ***suppression*** (**Adrenal** ***Insufficiency***).

Long term **use** ***high doses*** of **Glucocorticoids**; ***suppress*** **pituitary release** of **ACTH**, **Growth Hormone (GH)**, **Thyroid-stimulating Hormone (TSH)** and **Luteinizing Hormone (LH)**.

- ***Gradual dosing*** *example*;
  - **Methylprednisolone Dose-pack®**: **4 mg/tab**.
    - **Day 1**: 24 mg orally (8 mg before breakfast; 4 mg after lunch; 4 mg after dinner; 8 mg at bedtime).
    - **Day 2**: 20 mg orally (4 mg before breakfast; 4 mg after lunch; 4 mg after dinner; 8 mg at bedtime).
    - **Day 3**: 16 mg orally (4 mg before breakfast; 4 mg after lunch; 4 mg after dinner; 4 mg at bedtime).
    - **Day 4**: 12 mg orally (4 mg before breakfast; 4 mg after lunch; 4 mg at bedtime).
    - **Day 5**: 8 mg orally (4 mg before breakfast; 4 mg at bedtime).
    - **Day 6**: 4 mg orally (4 mg before breakfast).

- ***Uses***;
  - **Replacement *Therapy*** for;
    - ***Primary*** (**Cortisol *deficiency***) **adrenocortical insufficiency** (**Addison's disease**); *see next*.
    - ***Secondary*** (**ACTH *deficiency***) or ***tertiary*** (**CRH *deficiency***) **adrenocortical insufficiency**.
    - **Congenital Adrenal Hyperplasia** (**CAH**); ***congenital*** **mutations** of **genes** for **enzyme** ***mediating*** the **synthesis** of **one** or **more** of the **adrenal steroid hormones**.
  - ***Diagnosis*** of **Cushing's syndrome**; **Dexamethasone *suppression* test**;
    - **Dexamethasone *suppresses* Cortisol *release*** in ***normal*** **individuals**, ***but*** **not** those with **Cushing's syndrome**.
  - **Anti-inflammatory/Immunosuppressive *Therapy***; *such as* **rheumatoid arthritis**, **asthma exacerbations**, **inflammatory skin conditions**, **active inflammatory bowel disease**, ***acute*** **flare** of **gout** and **osteoarthritis** and ***prevent*** **rejection** in **organ transplantation**.
  - ***Treatment*** of **Allergic Reactions**; *such as* **allergic rhinitis**, **asthma**, **dermatitis** and **urticaria**.
  - ***Accelerate*** of **Fetal Lung Maturation** (**Antenatal Steroid**); When **delivery** is ***anticipated*** *before* **34 weeks** of ***gestation***;
    - **IM Betamethasone 12 mg 2 doses** *given* **24 hours** ***apart*** OR
      IM Dexamethasone 6 mg 4 doses *given* **12 hours apart**.
    - **Betamethasone** is ***preferred*** *but* the recommended formulation for preterm birth is a ***less*** **available** (mixture of long-acting betamethasone acetate and fast acting betamethasone phosphate; Celestone® Soluspan®).
    - **Optimal benefit *begins* 24 hours** after initiation of therapy and ***lasts* 7 days**.
  - **Cancer *Therapy*** (**Prednisone**); *such as* **Acute Lymphocytic Leukemia** and ***both*** **Hodgkin** and **non-Hodgkin Lymphomas**, **Multiple Myeloma** and ***other*** **Blood Cancers**;
    - **Prednisone** also **helps** to ***decrease*** **nausea** as well as ***promote*** an **appetite**.
  - **Nausea** and **vomiting**; A ***large dose*** of **Dexamethasone** ***reduces*** **emetic effects** of **chemotherapy** and **general anesthesia**.
  - **N.B.**; - ***Short-term*** **use** of **Glucocorticoids**, can ***potentiate*** **renal responsiveness** to **diuretic therapy** in patients with **heart failure**.
    - **Glucocorticoids** is ***symptomatically*** **effective** in ***malignant*** **exophthalmos**, ***subacute*** **thyroiditis**.
- ***Side Effects*** (**Cushing's Syndrome**);
  - **Hypothalamic–pituitary-adrenal axis** ***suppression***.
  - ***Inhibition*** of **leukocyte** and **monocyte** *function*.
  - **Skeletal muscle** ***myopathy***.
  - **Aseptic necrosis** of **bone**.
  - **Osteoporosis/fractures**.
  - **Pseudotumor cerebri**.
  - **Sodium** and **water retention**.
  - **Hypokalemia/hyperglycemia**.
  - **Hypertension**.
  - ***Impaired*** **wound healing**.
  - **Posterior subcapsular cataracts**.
  - **Glaucoma**.
  - **Central redistribution** of **fat**.
  - **Moon facies** and **buffalo hump**.
  - **Skin striae**.
  - **Pancreatitis**.
  - **Psychiatric disturbances**.
  - **Growth** ***retardation***.



Precautions and PATIENT COUNSELLING # # # # # #

1) **Sudden withdrawal *should be* avoided.**
2) **Corticosteroids regimen *should be gradually* decreased.**
3) ***Consider* use *dosing* *during* the maximal adrenal cortex activity *time*, to *avoid* suppress *endogenous* corticosteroids *secretions*; BEST TIME *between* 6-8 AM.**
4) ***Intake of* high protein diet to *prevent* muscle wasting.**
5) ***Intake of* high Calcium *supplementation* to *prevent* osteoporosis.**
6) ***Intake of* high vitamin B & vitamin D *supplementation* due to deficiency by long therapy.**
7) ***Intake of* *fresh* orange, banana juice or K^+ *supplementation* or oral rehydration therapy to *correct* hypokalemia.**
8) ***Protect* stomach by *using* corticosteroids *after* meal or *using* H_2 blockers or PPIs.**
9) **MONITORING; *signs for* infection, blood pressure, blood glucose, growth (length) *in children* and weight.**

Glucocorticoid Synthesis Inhibitors & Glucocorticoid Antagonists

Aminoglutethimide (Cytadren®)

Aminoglutethimide is an **anti-steroid drug** act by ***block*** the ***conversion*** of **Cholesterol** *to* **Pregnenolone**; ***reduction*** in the **synthesis** of ***all* hormonally *active* steroids.**
It is ***used*** for **Cushing's syndrome** and **metastatic breast cancer.**
- ***Side effects*; skin rash, hepatotoxicity** and **hypothyroidism.**

Ketoconazole (Nizoral®)

- **Ketoconazole** is an **antifungal *imidazole* derivative.**
- It is a **potent *non-selective* inhibitor** of **adrenal** and **gonadal steroid *synthesis*.**
- It is ***used*** for **Cushing's syndrome** (200-1200 mg/day orally) due to ***hepatotoxicity* dose *should be* started *slowly*** (200 mg) and **increased *gradually*** (200 mg/d every 2–3 days up to a total daily dose of 1000 mg).

Abiraterone (Zytiga®)

Abiraterone is an ***antiandrogen agent*** used in the **treatment** of **prostate cancer.**
- It ***blocks* 17α-hydroxylase** (P450c17) and **17,20-lyase**, and *predictably* ***reduces synthesis*** of **Cortisol** in the **adrenal** and **Gonadal Steroids** in the **gonads.**

Etomidate (Amidate®)

- **Etomidate** is a ***short-acting* IV anaesthetic *agent* *used*** for the ***induction*** of **general anaesthesia** and **sedation.**
- At ***subhypnotic* doses** (0.1 mg/kg per hour) **Etomidate *inhibits* adrenal steroidogenesis.**
- It is the ***only* parenteral** medication available in the ***treatment*** of ***severe* Cushing's syndrome.**

Metyrapone (Metopirone®) | Trilostane (Vetoryl®) | Mitotane (Lysodren®)

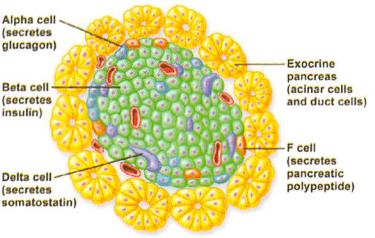
- They are a ***steroidogenesis inhibitor***, are **used** in **Cushing's syndrome.**

Mifepristone (Mifeprex®)

Mifepristone is an ***antiprogestogen***, as *well as* an ***antiglucocorticoid*** and ***antiandrogen*** to a *much* ***lesser* extent.**
Mifepristone is **abortifacient drug** used in ***combination*** with **Misoprostol** in **abortion.**
Mifepristone is used to ***control* hyperglycemia** (secondary to hypercortisolism) in patients with ***endogenous* Cushing's syndrome** who have **type 2 diabetes mellitus** or **glucose intolerance** and who **failed surgery** or who are ***not* surgical candidates.**
Mifepristone is also used for **emergency contraception** (taken after sexual intercourse).

Insulin and Antidiabetic Drugs

- **Pancreatic Tissues**;
  - **A) Pancreatic acini**;
    - **Exocrine** *part* (*About* **80%** of the **pancreas volume**).
    - ***Secrete* pancreatic juice *into*** the **duodenum**.
  - **B) Pancreatic islets** or **islets** *of* **Langerhans**;
    - **Endocrine** *part* (**1-2%** of the **pancreas volume**).
      - **Alpha** (α) **cells** (20% of total islet cells); **Glucagon**.
      - **Beta** (β) **cells** (≈70%); **Insulin** & **Amylin** (100:1).
      - **Delta** (δ) **cells** (<10%); **Somatostatin**.
      - **PP** (γ or **F**) **cells**; (<5%); **Pancreatic Polypeptide**.
      - **Epsilon cells** (<1%); **Ghrelin**.
        - **Ghrelin** (**hunger hormone**); produced by **GIT** and ***regulate*** **appetite** in **CNS** by ***inducing*** **hunger**.
        - **Leptin**; *produced by* **adipose cells** & ***regulate*** **energy balance** by ***inhibiting*** **hunger** (***opposite*** to **Ghrelin**).



Glucagon

Glucagon

Glucagon effect is ***opposite to*** that of **Insulin**, which ***lowers*** the ***extracellular* Glucose**.
- **Glucagon** ***acting*** *through* **G protein-coupled receptors** (*via* **cAMP**) in **heart**, **smooth muscle** and **liver**.
- ***Function***; ***increases*** **heart rate** and **force** of **contraction**, ***increases*** **hepatic glycogenolysis** and **gluconeogenesis**, and ***relaxes*** **smooth muscle** *particularly* in the **gut**.

Uses; It is **used IM** or **IV** to ***treat* severe hypoglycemia** (**Hypoglycemia Antidotes**), **β-blocker** and **calcium channel blocker toxicity** (increases cardiac cAMP without requiring access to β receptors), and **GI Radiography** (decrease GI motility).

Amylin

Amylin is a ***synergistic* partner** to **Insulin**, it ***regulate*** **blood glucose** by ***slowing*** **gastric emptying**, **promoting satiety** (via hypothalamic receptors), and ***inhibiting*** **inappropriate** ***secretion*** of **Glucagon**.
Pramlintide (**Symlin®**) is an ***injectable* amylin *analogue*** drug for **diabetes** (both **type 1** & **2**).

Insulin

Insulin is ***synthesized*** *as* the **prohormone Proinsulin**, an **86-amino-acid** ***single-chain*** **polypeptide**.
Proinsulin = **Insulin** (**A** + **B chain**; **51 amino acids**) + **C peptide** (**31 amino acids**).
Insulin is a ***dimer*** *of* **51 amino acids**; an **A-chain** and a **B-chain**, which are ***linked together*** by **disulfide bonds**.
C-peptide has ***no influence*** on **Glucose** or **Lipid** ***metabolism***, *but* have **beneficial** ***effects*** on **peripheral nerves**, **kidneys**, and **brain** (***protection*** *from* **diabetes complications**; **retinopathy**, **nephropathy** and **neuropathy**).
Insulin is **storage** in **granules** ***within*** the **β-cells** as ***insoluble*** **crystalline Hexameric-Insulin**.

Mechanism of Insulin Release;

- Glucose is the ***primary*** **stimuli** for Insulin ***release***.
- Glucose ***enters*** the **β-cells** through the **glucose transporters**, GLUT2 *via* **facilitated diffusion**.
- Glucose is ***phosphorylated***, ***high-energy*** ATP ***closes*** the **ATP-sensitive potassium channel**, *leading to* **depolarization**.
- *Upon* **depolarization**, **voltage-gated calcium channels** ***open***.
- An ***increased*** **intracellular** Ca^{2+} *leading to* ***increase*** Insulin ***secretion***.

Glucose Transporters		
Transporter	**Tissues**	**Function**
GLUT 1	All tissues especially red cells and brain	Transport across BBB
GLUT 2	Beta cells of pancreas, liver, kidney and gut	Regulation of insulin release
GLUT 3	brain and placenta	Uptake into neurons and other tissues
GLUT 4	Muscles and adipose tissues	Insulin-mediated uptake of glucose
GLUT 5	Gut and kidney	Absorption of fructose

Regulation of Insulin Secretion;

A) Blood Glucose;

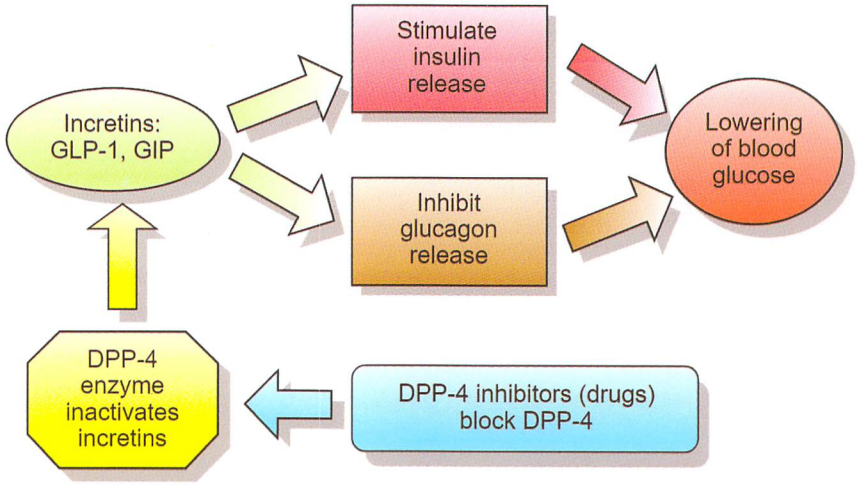
- Glucose is the ***primary*** **stimuli** for Insulin ***release***.
- ↑ ***blood*** Glucose ***level*** → ↑ Insulin ***secretion***.
  - Glucose ***does not*** **require** Insulin ***action*** to ***enter*** the **β-cell** (*due to* the Glucose is **transported** ***across*** GLUT2).

B) Amino Acids;

- **Amino acids** *such as* **Arginine** (cationic amino acid, which leads to membrane depolarization), **Alanine**, **Leucine** and **Glutamine** (via the Krebs cycle to generate ATP) → ↑ Insulin ***secretion***.

C) Gastrointestinal Hormones;

- Glucagon-like Peptide-1 (GLP-1) & Gastric Inhibitory Peptide [or Glucose-dependent Insulinotropic Peptide] (GIP) are **Incretins** and **released** ***after*** **eating** → ↑ Insulin ***secretion*** and ↓ Glucagon ***secretion***.
- ***Both*** GLP-1 & GIP are ***rapidly*** **inactivated** by **dipeptidyl peptidase-4** (DPP-4).



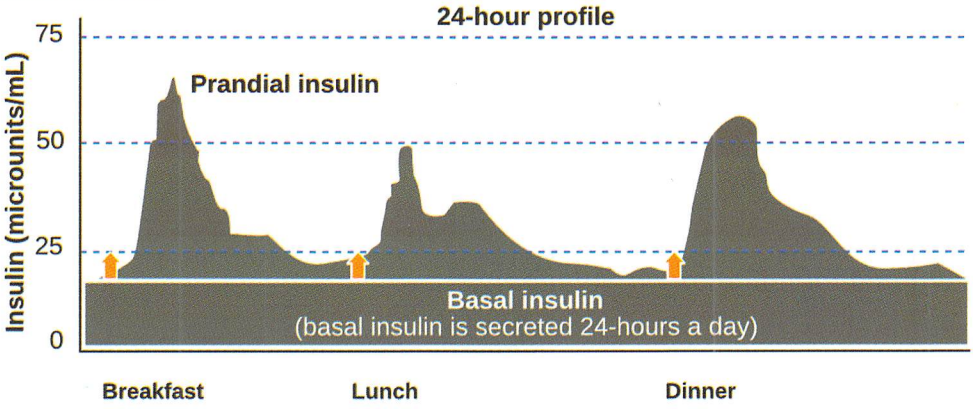
D) Autonomic Nervous System;

- Sympathetic; → ***strongly*** ↓ Insulin ***release*** (*via* **α_2 adrenergic receptors**).
  → ***minor*** ↑ Insulin ***release*** (*via* **β_2 receptors**).
- Parasympathetic; ↑ Insulin ***release*** (*via* **M_3 receptors** *through* **vagus nerve**).

E) Drugs;

- **Sulfonylurea drugs** → ↑ Insulin ***release***.

Insulin *Release*;



Basal insulin; is the **insulin** *normally* ***supplied by*** the **pancreas** and is ***present*** **24 hours a day**, whether or not the person eats; **50%** of ***total*** **daily Insulin** ***release***.

Bolus insulin; is the ***extra amounts*** of **insulin** ***supplied by*** the **pancreas** in ***response*** to **glucose taken** in *through* **food** (The amount of bolus insulin produced ***depends on*** the **amount of meal**).

Insulin *Function*;

A) **Carbohydrate Metabolism**;

Stimulates **glucose** ***uptake*** in **muscles** and **fat tissues**; by insertion of the GLUT4 transporter in the cell membranes.

Increase **glycogenesis**; by Increase activity of glycogen synthase.

Increase **glycolysis** and ***decrease*** **gluconeogenesis**.

B) **Lipid Metabolism** [↑ Lipogenesis and ↓ Lipolysis];

Stimulates **fatty acid** ***synthesis*** in **adipose tissue**, **liver** and **lactating mammary glands**; by increase activity of acetyl-CoA carboxylase.

Stimulates **triglyceride** ***synthesis*** in **adipose tissue** and **liver**; by increase esterification of fatty acid with glycerol.

Stimulates **cholesterol** ***synthesis***; by increase activity of HMG Co-A reductase.

Inhibit **ketogenesis** (ketone bodies formation); by inhibits lipolysis.

- **Ketone bodies** are ***particularly*** **important** for the **brain** which has ***no other*** **substantial** ***non*-glucose-*derived*** **energy source**.
- **Ketone bodies** are **Acetoacetate**, **β-hydroxybutyrate** (or **3-hydroxybutyrate**) and **Acetone**.
- **Ketone bodies** are ***increase*** *during* **fasting** and ***prolonged*** **exercise**.
- **Diabetes** is the ***most*** **common pathological cause** of ***elevated*** **blood ketones**.
- **Ketone bodies** are **acidic**, and, if **levels** of these **ketone bodies** are ***too high***, the **pH** of the **blood** ***drops***, resulting in **ketoacidosis**.
- **Diabetic ketoacidosis** (**DKA**) is a *potentially* ***life-threatening*** **complication** of **diabetes mellitus**.

C) **Protein Metabolism** [Anabolic];

Increase **amino acid** ***uptake***.

Promotes **protein synthesis** and ***decrease*** **proteolysis** (protein breakdown).

- N.B.; - Insulin can bind to the receptors for IGF-1 but with much lower affinity and IGF-1 binds weakly to the insulin receptor.
- Insulin-like growth factors (IGF) are so-called because they have significant structural homology with proinsulin.

Insulin Resistance

Insulin Resistance (**IR**); ***reduced*** **biological response** to **Insulin**.

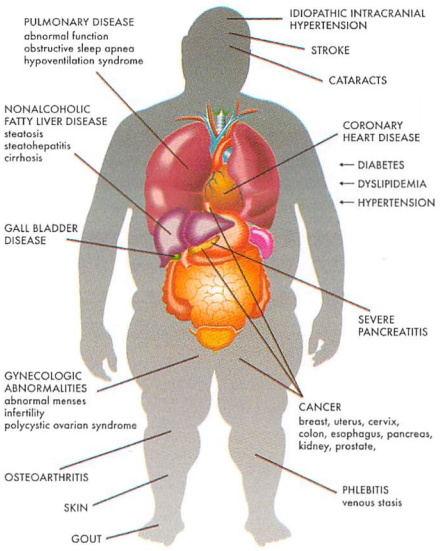
Causes;

A) Pre-receptor;
- ***Abnormal*** **insulin** (mutations).
- **Anti-insulin antibodies**.

B) Receptor;
- ***Decreased*** **number** of **receptors** (mainly, failure to activate tyrosine kinase).
- ***Reduced*** **binding** of **insulin**.
- **Insulin receptor *mutations***.
- **Insulin receptor–*blocking* antibodies**.

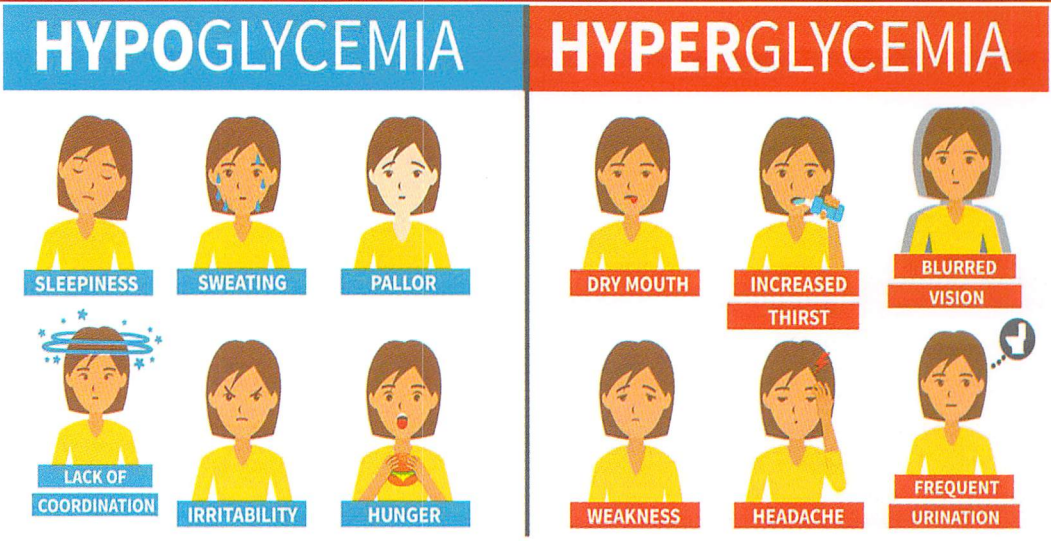
C) Post-receptor;
- ***Defective*** **signal transduction**.
- ***Mutations*** of **GLUT4** (rare).

Specific conditions;
- **Aging**; (decreased production of GLUT-4).
- **Cushing syndrome**, **acromegaly** and **stress states**.
- Medications; **Glucocorticoids**, **Cyclosporine**, **Niacin** and **Protease Inhibitors**.
- ***High*** **sodium intake**; ↑ Glucocorticoid production.
- **Insulin therapy**: Low-titer anti-insulin antibody.



Conditions Associated with Insulin Resistance

Disturbance of Insulin Hormone Functions



Diabetes Mellitus (DM)

Diabetes Mellitus (**DM**) is a **disease state** that ***results*** in an *inappropriately* ***high*** **blood sugar levels** ***over*** a **prolonged** ***period***.

There are **3** ***main*** **types** of **diabetes mellitus**:

1) Type 1 DM; ***results from*** the **pancreas's** ***failure*** to **produce** ***enough*** **insulin**.

2) Type 2 DM; *begins with* **insulin resistance** (cells fail to respond to insulin properly).

3) Gestational diabetes; *occurs* when **pregnant women** ***without*** a ***previous*** **history** of **diabetes** *develop* ***high*** **blood sugar** ***levels***.

Main Symptoms; (* Classical Symptoms).

* **Polyphagia** (frequent hunger)
* **Polydipsia** (frequent thirst)
* **Polyuria** (increased volume of urination).
* ***Unexplained* weight loss**.
- **Diabetic Ketoacidosis (DKA)**; **Fruity (Acetone)** ***smelling*** **breath odour**.
- **Lethargy**.

Diagnosis;

Diagnostic Criteria	Random Plasma Glucose (mg/dL)	Fasting Plasma Glucose (mg/dL)	2-Hour Post-glucose (75 g) Load (mg/dL)	Glycated Hemoglobin [A1C] (%)
Prediabetes		100–125	140–199	5.7–6.4
Diabetes	≥ 200 (with symptoms)	≥ 126	≥ 200	≥ 6.5

Renal Threshold of **Glucose** (**RTG**); When the **blood glucose level** ***exceeds*** about **160–180 mg/dL**, the **proximal tubule** *becomes* ***overwhelmed*** and **begins** to ***excrete*** **glucose** in the **urine**.

- ***Causes*** and ***Risk Factors***;

	Type 1 DM	**Type 2 DM**
Causes	[Insulin Deficiency] - ***Autoimmune*** **destruction** of **insulin-producing beta cells** of **pancreas**. - ***Most common*** **type** in **children**.	[Insulin Resistance] - ***Defective*** **responsiveness** of **body tissues** to **insulin**. - ***Common*** **type** in **adult**.
Risk factors	1) **Genetics**; > 50 genes are associated. 2) **Dietary factors**; - ***Low*** **vitamin D** ***consumption***. - ***Early*** **exposure** (infancy) to **cow's milk** 3) **Viral infection**; such as enterovirus infections, mumps and rubella. 4) **Cytotoxic drugs** and **chemicals**; - **Pyrinuron**; *rodenticide* - **Streptozocin**; *antineoplastic*. 5) **Geography**; European populations, with people from northern Europe more often affected than those from Mediterranean regions and least prevalent in East Asians.	1) **Family history** *of* **type 2 DM**. 2) **Age** ***greater than*** **45 years**; risk ↑ in older; testing should be done. 3) ***Over*** **Weight**; greater than 120% of desirable body weight; more fatty tissue more resistant to insulin. 4) **Polycystic Ovarian Syndrome**; which results in insulin resistance. 5) ***History*** of **gestational diabetes**. 6) **Hypertension** or **dyslipidemia** 7) **Inactivity**; *leads to* impaired glucose control 8) **Race**; Hispanic, Native American, African American, Asian American, or Pacific Islander descent.

- **Vitamin D** ***deficiency*** are ***linked to*** **Type 1 DM** in ***children***, **Type 2 DM** and **Gestational Diabetes**.

Diabetic Complications; *If* **blood sugar levels** ***well*-controlled**, the **complications** of **diabetes** are *far* ***less*** **common** and ***less*** **severe**.

Acute Complications;

Hypoglycemia; More severe and can cause brain damage and death.

- Treated with sugary drinks as soon possible and IV infusion of dextrose.
- In severe cases treated with IV glucagon.

Diabetic Ketoacidosis (DKA); **Predominant symptoms**; **nausea** and **vomiting**, **thirst**, ***excessive*** **urine production** and **abdominal pain** that may be ***severe***.

- In ***severe*** **DKA**;
  - Breathing becomes rapid and of a deep, gasping character, called "Kussmaul breathing" with fruity (Acetone) smelling breath odour.
  - Confusion or a marked decrease in alertness, including coma.
  - The primary treatment of DKA is with IV fluids and insulin (IV or SC depending on severity), sodium bicarbonate may be given.
  - Death can result from inadequate or delayed treatment, or from complications (e.g., brain edema especially in children).

Hyperglycemia Hyperosmolar State (HHS);
- HHS is characterized by hyperglycemia, hyperosmolarity and dehydration without significant ketoacidosis.
- Hyperglycemia → glucosuria (renal threshold; >180 mg/dL) → loss of more water than sodium (excessive urination; osmotic diuresis) leads to → hyperosmolarity → dehydration → weakness, legs cramps, trouble seeing, risk of blood clotting (hyperviscosity), and an altered level of consciousness or coma.
- The primary treatment of HHS is IV fluids and insulin; potassium replacement and heparin (decrease the risk of blood clotting) may be given.

Diabetic Coma; Severe hypoglycemia, DKA and HHS.

Chronic complications;

Microangiopathy;

***Diabetic* Nephropathy**; damage to the kidney which can lead to chronic renal failure.

***Diabetic* Neuropathy**; abnormal and decreased sensation, starting with the feet but potentially in other nerves, later often fingers and hands.

***Diabetic* Retinopathy**; damage to the small blood vessels and neurons of the retina and may develop macular edema (swelling of the macula), which can lead to severe vision loss or blindness.

- ***Others***; diabetic cardiomyopathy and encephalopathy, erectile dysfunction and Periodontal disease (gum disease).

Macrovascular Disease; **Coronary artery disease**, **peripheral vascular disease**, **diabetic foot** and **female infertility**.

Immune Dysfunction; Infections & autoimmune diseases such as leukocytoclastic vasculitis.

Treatment of **Diabetes**;

A) Life-Style Modifications; All people with diabetes should participate in diabetes self-management education (DSME) and diabetes self-management support (DSMS) programs to facilitate the knowledge, skills, and abilities necessary for optimal diabetes self-care and incorporate the needs, goals, and life experiences of the person with diabetes.

- **Weight Management**; can delay the progression from prediabetes to type 2 diabetes.
- **Alcohol Consumption**; risk of hypoglycemia weight gain and hyperglycemia.
- **Nutrition Therapy**;
  * **Carbohydrate**; Education on how to use **Carbohydrate Counting**;
    - Help patients with diabetes plan meals.
    - Patients need to be aware of the amount of carbohydrates they eat.
    - Patients count all the carbohydrates in each meal and snack they eat.
    - Able to adjust their insulin dose according to the amount of carbohydrates eaten.
    - Allows for better blood glucose control.
  * **Protein**; Ingested protein appears to increase insulin response without increasing plasma glucose concentrations; should not be used to treat or prevent hypoglycemia.
  * **Dietary fat**; foods rich in long-chain omega-3 fatty acids is recommended to prevent or treat CVD.
  * **Sodium**; people with diabetes should limit sodium consumption to 2,300 mg/day.
  * **Nonnutritive Sweeteners**; reduce overall calorie and carbohydrate intake.
- **Physical Activity**; improve blood glucose control, reduce cardiovascular risk factors, contribute to weight loss, and improve well-being.
- **Smoking Cessation**; Tobacco and e-cigarettes; heightened risk of diabetic complications.

B) Medications;

- **Insulin**: *for* **Type 1** and **Type 2 DM**.
- **Metformin** , **Incretin Mimetics** and **Oral Antidiabetic Drugs**; *for* **Type 2 DM**.

Antidiabetic Drugs

I) Insulin

Regular Insulin (Humulin® R)
Insulin Aspart (NovoRapid®)
Insulin Lispro (Humalog®)
Insulin Glulisine (Apidra®)
Insulin NPH (Insulatard®)
Insulin Glargine (Lantus®)
Insulin Detemir (Levemir®)
Insulin Degludec (Tresiba®)
Inhalable Insulin (Afrezza®)

II) Insulin Secretagogues

Sulfonylureas

First Generation
Tolbutamide (Orinase®)
Tolazamide (Tolinase®)
Acetohexamide (Dymelor®)
Chlorpropamide (Diabinese®)
Carbutamide (Glucidoral®)

Second Generation
*__Glibenclamide__ or **Glyburide** (Daonil®)
*__Glimepiride__ (Amaryl®)
*__Glipizide__ (Minidiab®)
*__Gliclazide__ (Diamicron®)
Gliquidone (Glurenorm®)
Glibornuride (Glutril®)
Glyclopyramide (Deamelin-S®)

Meglitinides
*__Repaglinide__ (NovoNorm®)
*__Nateglinide__ (Starlix®)
Mitiglinide (Glufast®)

III) Insulin-Sensitizers

Biguanides
Metformin (Glucophage®)

Thiazolidinediones
Pioglitazone (Actos®)
Rosiglitazone (Avandia®)

Glitazars
Saroglitazar (Lipaglyn®)

IV) Peptide Analogues

Injectable **Incretin Mimetics [Glucagon-like peptide-1 Agonists]**
Exenatide (Byetta®)
Liraglutide (Victoza®)
Lixisenatide (Lyxumia®)
Albiglutide (Tanzeum®)
Dulaglutide (Trulicity®)
Semaglutide (Ozempic®)

Dipeptidyl Peptidase-4 Inhibitors
Sitagliptin (Januvia®)
Vildagliptin (Galvus®)
Saxagliptin (Onglyza®)
Linagliptin (Tradjenta®)
Alogliptin (Nesina®)

Injectable **Amylin Analogues**
Pramlintide (Symlin®)

V) Glycosurics

Sodium/Glucose Co-transporter-2 (SGLT2) Inhibitors
Dapagliflozin (Farxiga®) (Forxiga®)
Canagliflozin (Invokana®)
Empagliflozin (Jardiance®)
Ertugliflozin (Steglatro®)

VI) Alpha-glucosidase Inhibitors

Acarbose (Glucobay®)
Miglitol (Glyset®)
Voglibose (Voglib®)

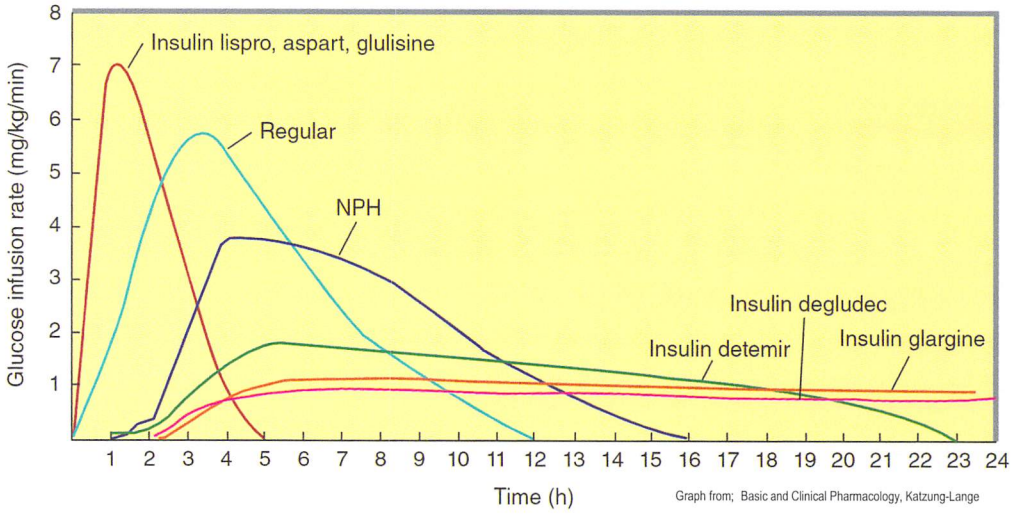
VII) Others

Bile Acid Sequestrants
Colesevelam (Welchol®)

Dopamine Agonists
Bromocriptine (Cycloset®)

I) Insulin Preparations

Preparation		Species Source	Pattern
Short-acting Insulin	Regular Human Insulin	Human	Bolus
Rapid-acting Insulin	Insulin Aspart Insulin Lispro Insulin Glulisine	Human Analogue	Bolus
Intermediate-acting Insulin	Neutral Protamine Hagedorn (NPH)	Human	Bolus/Basal
Premixed Insulin	NPH/Regular Protamine/Rapid-acting	Human Human Analogue	Bolus/Basal
Long-acting Insulin	Insulin Glargine Insulin Detemir Insulin Degludec (ultra-long)	Human Analogue	Basal

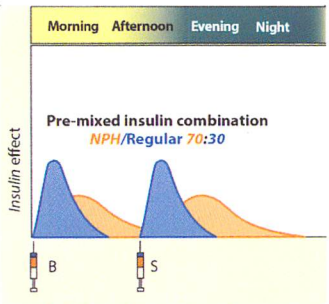


Graph from; Basic and Clinical Pharmacology, Katzung-Lange

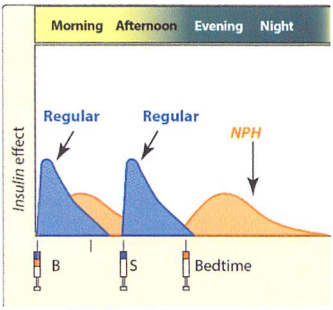
- **Total Daily Dose** (**TDD**) **Insulin** ***requirement***; *Initially*; **0.3–0.5 unit/kg/day**.
- ***Generally***, to ***correct*** a **high blood sugar**, **1 unit** of **Insulin** is ***needed*** *to* ***drop*** the **blood glucose** by **50 mg/dl**.

[**Basal/Bolus Insulin regimen** is ***recommended***]

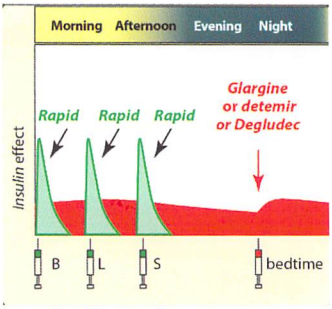
- **Multiple Daily Injection** (**MDI**) ***Regimen***;



2 injections per day



3 injections per day



≥ 4 injections per day

* ***Long-acting*** **Insulin** in a **basal/bolus regimen** in **≥ 4-injection regimen**; *About* **50%** of **TDD**.

Insulin Pens

- **Disposable pen**; Contains a **prefilled** insulin cartridge. Once used, the entire pen unit is thrown away.
- **Reusable pen**; Contains a **replaceable** insulin cartridge. Once empty, a person discards the cartridge and installs a new one.

Pen type	Company	Use	Insulin used
KwikPen®	Eli Lilly	Disposable/Reusable	Humalog®
FlexPen®	Novo Nordisk	Disposable	Levemir® - NovoRapid® Novolog® - NovoMix®
FlexTouch®	Novo Nordisk	Disposable	Fiasp® - Levemir® Tresiba® - Ryzodeg®
NovoPen® 4 & 5 NovoPen Echo®	Novo Nordisk	Reusable	Levemir® - NovoRapid® Novolog® - NovoMix® Tresiba® - Ryzodeg®
Solostar®	Sanofi-Aventis	Disposable	Lantus® - Toujeo® - Apidra®
AllStar®	Sanofi-Aventis	Reusable	Lantus® - Toujeo® - Apidra® Insuman®

Insulin Pen Needle (most common)

Needle type	Pen Type
BD Microfine Needles BD Ultra-Fine Nano Pen Needles	Universal Fit
NovoFine Pen Needles	Novo Nordisk Pens

A) Short Acting Insulins (Natural insulin)

Soluble Insulin or Regular Insulin (Humulin® R)# (Actrapid®)# (Insuman®)

Soluble Insulin or **Regular Insulin** is a ***soluble*** **crystalline Zinc Insulin** that is *made by* **rDNA techniques** (**Clear Insulin**).

Pharmacokinetics; - ***Onset***; 30-60 minutes. - ***Peak***; 2-4 hours. - ***Duration***; 4-8 hours.

Uses; - **Used** to ***control*** the **Postprandial Hyperglycemia** (**Bolus ONLY**).

Regular Insulin can be used as **IV** in **emergency**.

- ***Time of Administration***; # **30-60 minutes *before* meal.**

☝ **Patient *must* eat** (to ***avoid*** **hypoglycemia**).

B) Rapid Acting Insulins (Insulin analogue)

Insulin Aspart (NovoRapid®)# (Fiasp®) (Novolog®) | **Insulin Lispro** (Humalog®)#

Insulin Glulisine (Apidra®)#

Insulin Aspart is an **Insulin *analogue*** in *which* a ***single*** **substitution** of **Proline** by **Aspartic acid** at ***position*** **B28**.

Insulin Lispro the **Proline** at ***position*** **B28** is ***reversed*** *with* the **Lysine** at **B29**.

Insulin Glulisine **differs *from human* Insulin** in that the **amino acid Asparagine** at ***position*** **B3** is ***replaced by*** **Lysine** and the **Lysine** in ***position*** **B29** by **Glutamic Acid**.

They are ***preferred*** to **Regular Insulin** *because* of ***faster*** **onset** and ***shorter*** **duration**, ***better*** **mimicking physiological need** ***during*** **postprandial period**.

Pharmacokinetics;

- **Insulin Aspart**; - ***Onset***; 5-15 minutes. - ***Peak***; 1-2 hours. - ***Duration***; 3-5 hours.
- **Insulin Lispro**; - ***Onset***; 5-15 minutes - ***Peak***; 0.5-2 hours. - ***Duration***; 3-5 hours.
- **Insulin Glulisine**; - ***Onset***; 15-20 minutes. - ***Peak***; 0.75-1 hours. - ***Duration***; 4-5 hours.

Uses; # **Used** to ***control*** the **Postprandial Hyperglycemia** (**Bolus ONLY**).

Insulin Aspart can be used as **IV** in **emergency**.

- ***Time of Administration***; # **5-15 minutes *before* meal**; **just before** or **with** a **meal**.

☝ **Patient *must* eat** (**Act *very quickly*** **hypoglycemia** *occur* if ***not*** **eat**).

C) Intermediate Acting Insulins (Neutral Protamine Hagedorn –NPH or Isophane)

Insulin NPH (Insulatard®)# (Humulin® N)#

- In 1936, Hagedorn and B. Norman Jensen discovered that the effects of injected insulin could be prolonged by the addition of protamine, so that neither is present in an uncomplexed form (Isophane). After subcutaneous injection proteolytic tissue enzymes degrade the protamine to permit absorption of insulin.

Neutral Protamine Hagedorn (NPH) is a ***suspension*** (**Cloudy/milky**) of ***crystalline*** **Zinc Insulin** ***combined with*** the *positively* ***charged*** *polypeptide* **Protamine**; ***less*** **soluble**, resulting in ***delayed*** **absorption** and a ***longer*** **duration** of **action**.

Pharmacokinetics; - ***Onset***; 1-2 hours. - ***Peak***; 5-10 hours. - ***Duration***; 10-16 hours.

Uses; used for **basal** ***coverage***.

NPH and **Protamine** are *usually* ***mixed*** with **Regular**, **Lispro**, **Aspart**, or **Glulisine Insulin**;

Premixed **Insulin**;

Mixtard® 70/30 or **Humulin®** 70/30	70% **NPH** + 30% **Regular**
Mixtard® 50/50	50% **NPH** + 50% **Regular**
NovoMix® Flexpen	70% **Protamine Aspart** + 30% **Aspart**
Humalog® Mix 75/25	75% **Protamine Lispro** + 25% **Lispro**
Humalog® Mix 50/50	50% **Protamine Lispro** + 50% **Lispro**

D) Long-acting Insulin

Insulin Glargine (Lantus®)#

Insulin Glargine is a ***peakless*** (plasma concentration is plateau = **Basal**), ***long-acting*** **Insulin** ***analogue***.

Pharmacokinetics;

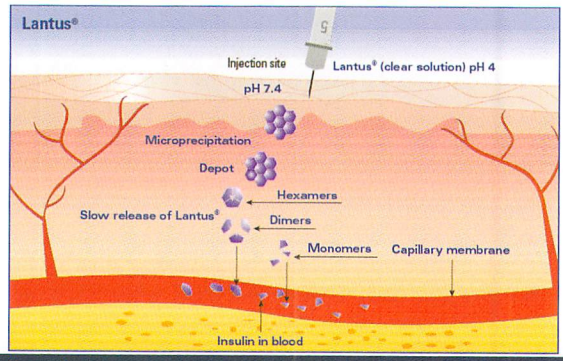
- ***Onset***; 2 hours. - ***Peak***; **Peakless** (max. effect after 2–4 hours) - ***Duration***; 20-24^{+} hours.

To ***maintain*** **solubility**, the ***formulation*** is **acidic** (pH 4.0), and **Insulin Glargine** ***should not*** be **diluted** or **mixed** with ***other*** **Insulin** or ***solution*** in the ***same*** **syringe**.

- **Glargine** is *usually* given **once daily** (Some patients on low doses require twice-daily dosing).

- **Injection-site reactions** (e.g., edema, itching, pain, stinging); because of acidic formulation.

- The amino acid asparagine at position A21 is replaced by glycine, and two arginines are added to the C-terminus of the B-chain. These changes shift the isoelectric point, producing a solution that is completely soluble at a pH of 4.
- When injected into the subcutaneous tissue, the acidic solution is neutralized (pH 7.4).
- This leads to the formation of microprecipitates, which small amounts of Lantus® are slowly released.
- The slow dissolution of free hexamers results in the lack of a peak and longer duration of action.



Insulin Detemir (Levemir®)#

Insulin Detemir is a ***long-acting*** **Insulin** ***analogue*** in which a **fatty acid** (**Myristic acid**) is *bound to* the **Lysine** **amino acid** at ***position*** **B29**. The **fatty acid** ***side chain*** that ***enhances*** **association** to **albumin**. ***Slow*** **dissociation** *from* **albumin** *results in* ***long-acting*** **properties**.

Pharmacokinetics;

- ***Onset***; 1-2 hrs. - ***Peak***; **Peakless** (max. effect after 4–8 hrs) - ***Duration***; 10-24 hrs.

Detemir ***should*** ***not*** be **diluted** or **mixed** with ***other*** **Insulin** or ***solution*** in the ***same*** **syringe**.

- ***Smoother*** **activity profile** and ***less*** **weight gain** *compared with* **NPH** and **Glargine**.
- It is ***used*** **once** or **twice** a day to *achieve* a ***stable*** **basal** **coverage**.

Insulin Degludec (Tresiba®)#

Insulin Degludec is an ***ultra-long-acting*** **Insulin** ***analogue*** in which a **Threonine** at ***position*** **B30** has been ***removed*** and the **Lysine** at ***position*** **B29** is ***conjugated to*** **hexadecanoic acid** via a **gamma-l-glutamyl** ***spacer***.

- **Insulin Degludec** was **FDA approved** in 25 September **2015**.

Duration of ***action*** is ***more than*** **42 hours** (***ultra-long-acting***).

- In the **vial**, in the presence of **Phenol** and **Zinc**, the **Insulin** is in the form of **dihexamers** ***but***, when ***injected*** **SC**, it *self-associates* into ***large*** **multihexameric** *chains consisting of* **thousands** of **dihexamers**.
- **Ryzodeg®** **70/30** is a **human insulin analog solution** ***containing*** **70%** **Insulin Degludec** and **30%** **Insulin Aspart**.

E) Inhaled Insulin

Inhalable Insulin (Afrezza®)#

A ***dry*** **powder** *formulation* of ***recombinant*** **Regular Insulin** is *now* ***approved*** for use in **adults** with **diabetes**.

After **inhalation**; ***peak*** **levels** are *reached* in **12–15 minutes** and ***decline*** to **baseline** in **3 hours**; ***faster*** in **onset** and ***shorter*** in **duration** than **SC** **Insulin**.

- It is ***formulated*** as a ***single-use*** **color** ***coded*** **cartridge** *delivering* **4**, **8** or **12 units** ***immediately*** *before* the **meal**;
  - 4-unit cartridge = 4 units of rapid-acting insulin.
  - 8-unit cartridge = 5–8 units of rapid-acting insulin.
  - 12-unit cartridge = 9–12 units of rapid-acting insulin.

II) Insulin Secretagogues

1) Sulfonylureas

First Generation

Tolazamide (Tolinase®)	**Acetohexamide** (Dymelor®)	**Carbutamide** (Glucidoral®)
Chlorpropamide (Diabinese®)	**Tolbutamide** (Orinase®)	

Second Generation

Glibenclamide or **Glyburide** (Daonil®)#	**Glimepiride** (Amaryl®)#	
Glipizide (Minidiab®)#	**Gliclazide** (Diamicron®)#	**Glibornuride** (Glutril®)
Gliquidone (Glurenorm®)	**Glyclopyramide** (Deamelin-S®)	**Glisoxepide**

These agents are classified as **insulin secretagogues**, *because* they ***promote* Insulin *release*** from the **β cells** of the **pancreas**.

The **sulfonylureas** in ***current*** **use** are the **second-generation *drugs*** (***good*** **pharmacokinetic profile**, ***more*** **potent** and ***less*** **side effects**).

Glyburide, **Glipizide** and **Glimepiride** are the ***only* sulfonylureas *currently*** *available* in **US**.

Dose (**Second-generation**); *usually* **once daily** *with* **breakfast** or ***first main* meal** of the day.

Glimepiride is ***approved*** for **once-daily use** as ***monotherapy*** or in ***combination*** with **Insulin**.

Micronized* Glyburide** (**Glynase® PresTab®**) is ***available (faster in onset).

Glipizide *extended-release* formulation (**Glucotrol XL®**) is ***available*** (provides 24-hour action after a once-daily morning dose).

Second-generations are *usually* ***combined*** with **Metformin**.

Major Side Effects; **Weight gain**, **hyperinsulinemia** and **hypoglycemia**.

Used with ***caution*** in **hepatic** or **renal insufficiency** (accumulation of sulfonylureas may cause hypoglycemia); - ***Increase*** the **risk** of **hypoglycemia** with **Glyburide** in **renal impairment**.
- **Glipizide** or **Glimepiride** are safer in renal dysfunction and in elderly patients.

Glyburide has ***minimal* transfer** *across* the **placenta** and *may be* **allowing** a **safe *new* treatment** for **Gestational Diabetes**.

Drug Interactions;

Drugs that ↓ **Sulfonylureas *effects***; **Atypical antipsychotics**, **Corticosteroids**, **Diuretics**, **Niacin**, **Phenothiazines** and **Sympathomimetics**.

Drugs that ↑ **Sulfonylureas *effects***; **Azole antifungals**, **β-blockers**, **Chloramphenicol**, **Clarithromycin**, **Monoamine Oxidase Inhibitors**, **Probenecid**, **Salicylates**, **Sulfonamides** & **Warfarin**

2) Meglitinides "Glinides"

Repaglinide (NovoNorm®)#	**Nateglinide** (Starlix®)	**Mitiglinide** (Glufast®)

This **class** of **drugs**, also *known as* the ***Non*-sulfonylurea Secretagogues**.

Meglitinides act on the ***same* β-cell receptor** as **Sulfonylureas** (same mechanism) *but* have a ***different* chemical structure** with ***rapid*** **onset** and a ***short*** **duration** of **action**;

No **sulfur** in its **structure**, so they may use in **type 2 diabetics** with **sulfur** or **sulfonylurea *allergy***.

NovoNorm® available as tablets (white: 0.5 mg; yellow: 1 mg; peach: 2 mg), dose; **15 minutes *before*** each main meal; max. daily dose: 16 mg per day;

Risk of **hypoglycemia** if **meal** is ***delayed*** or ***skipped*** or ***inadequate*** **carbohydrate**.

They are **metabolized** to **inactive *products*** by **CYP450**;
- **Nateglinide** → CYP2C9 and CYP3A4
- **Repaglinide** → CYP3A4; drug interactions

***Major* side effects**; **Weight gain** & **hypoglycemia** (less than sulfonylureas).

Meglitinides *should not* be **combined** *with* **Sulfonylureas**, *because* they have the ***same* mechanism** *of* **action**; ***risk*** of **hypoglycemia**.

III) Insulin-Sensitizers

1) Biguanides

Metformin (Glucophage®)#

The **Insulin-Sensitizers** are ***class*** of **drugs** that ***enhance*** the **Insulin** ***sensitivity*** in **peripheral tissues** (**muscle**, **fat** and **liver**); ***decrease*** **insulin resistance** and ***increases*** **glucose uptake**.

Unlike **Sulfonylureas**, **Insulin-Sensitizers** ***does not*** *promote* **Insulin secretion**;
- Therefore, hyperinsulinemia is not a problem, and less risk of hypoglycemia.

- **Metformin** is the ***only*** **biguanide** ***currently*** **available** (**Phenformin** and **Buformin** are ***withdrawn*** from the **market** *due to* **toxic effects**).

Metformin *act by* ***decrease*** **insulin resistance**;
* ***Suppressing*** liver **Glucose** ***production*** (↓ hepatic gluconeogenesis).
* ***Decreasing*** intestinal **absorption** of **Glucose**.
* ***Improving*** **Insulin** **sensitivity** by ***increasing*** peripheral **Glucose** ***uptake*** and ***utilization***.

Uses;
- **Type 2 Diabetes** (**first line therapy**; **all patients**).
 # Off-Label Uses; [***Decrease*** **Insulin** ***Resistance***];
- **Prediabetes**; decrease their chances of diabetes.
- **Gestational Diabetes** (*safe as* **Insulin**); **US FDA Category B**.
- **Polycystic Ovary Syndrome** (**PCOS**) and **Female Infertility**.
- ***Prevention*** of **weight gain** *caused by* **antipsychotic medications**.
- ***Not*** **yet** ***recommended*** *for* **weight loss**.
- ***Reduce*** **risk** of **pancreatic cancer**.
- ***Helps*** to ***reduce*** **LDL cholesterol** and **triglyceride levels**.

Formulations;
- **Metformin** **IR** (**immediate release**); 500, 850 and 1000-mg tablets.
- **Metformin** **SR** (**slow release**) or **XR** (**extended release**); 500, 750, and 1000-mg tablets; mainly to ***counteract*** *common* **GI side effects**.
- **Metformin** is available as **fixed-dose combinations** with ***other*** **oral antidiabetic drugs**.

Dose in **Type 2 Diabetes**;
- ***Prescribed*** as **maximum tolerated dose** (until GI side effects occur but not more than 2500 mg/day), ***start gradually***, **SR** or **XR** ***formulations*** has ***low*** **risk** for **GI side effects**.

Side effects; **Gastrointestinal Upset** (*including* **diarrhea**, **cramps**, **nausea**, **vomiting** and **flatulence**) occur in ***up to*** **20%** of **patients**; **dose titration** ***recommended*** to **develop tolerance**.

 # # Black Box Warning; **Lactic Acidosis** (**rare**, *but* ***potentially*** **severe**) **risk** ***increases*** in **patients** with ***severe*** **renal impairment**.

- ***Long-term*** use may ***interfere*** with **Vitamin B_{12}** ***absorption***.

2) Thiazolidinediones (TZDs) "Glitazones"

Rosiglitazone (Avandia®)#	Pioglitazone (Actos®)#

- **Pioglitazone** and **Rosiglitazone** are the ***only*** **Glitazones** ***still*** *available* in ***some*** **countries**.
- **Pioglitazone** (once daily) and **Rosiglitazone** (once daily OR 2 divided doses) are is *approved* as a ***monotherapy*** and in ***combination*** *with* **Metformin**, **Sulfonylureas** and **Insulin** for the ***treatment*** of **Type 2 Diabetes** (***not*** **first line**; **used** in **people** who ***can't*** **control** their **diabetes** by ***other*** **ways**).
- **TZDs** can **used** in ***combination*** *with* **Metformin** in **Polycystic Ovary Syndrome** (**PCOS**).
- **TZDs** are ***ligand*** of **peroxisome proliferator-activated receptor-gamma** (**PPARγ**), a ***group*** of **nuclear receptors** *found* in **muscles**, **adipose tissues** and **liver**.

Side effects;
- **Liver toxicity** has been *reported*; **Liver function tests** *should be* **performed**.
- **Fluid retention** (*worsen* **heart failure**) and **weight gain**.

Black Box Warning; *Risk of* **Congestive Heart Failure** in *some* **patients**.

Meta-analysis **Studies**;
* **Rosiglitazone** may *increase* **risk** of **Coronary Heart Diseases** (**angina** or **myocardial infarction**).
* **Pioglitazone** may *associated* with a *slightly* **higher risk** of **Bladder Cancer**.

Reduce of **bone mineral density** and *increase* the **risk** of **fractures** in **women**, due to *decreased* **osteoblast** *formation*.

3) Dual PPAR agonists "Glitazar"

Saroglitazar (Lipaglyn®)

- **Saroglitazar** is *novel first* in class **drug** which *acts* as a *Dual* **PPAR agonist** at the *subtypes* α and γ of the **peroxisome proliferator-activated receptor** (**PPAR**).
- **Saroglitazar** was *approved* in **2013** in **India** for the *treatment* of **Type 2 Diabetes** and **Dyslipidemia** (↑ **HDL cholesterol**, ↓ **LDL cholesterol** and ↓ **Triglycerides**).
- *Side Effects*; *According* to the **data** in the official website of the drug "lipaglyn.com", It has *no* or *less* **side effects** (weight gain and edema) *than* **TZDs**.

IV) Peptide Analogues

1) *Injectable* Incretin Mimetics [Glucagon-like Peptide-1 Agonists]

Exenatide (Byetta®)# (Bydureon®)	**Liraglutide** (Victoza®)# (Saxenda®)#
Lixisenatide (Lyxumia®)# (Adlyxin®)	**Albiglutide** (Tanzeum®)#
Dulaglutide (Trulicity®)#	**Semaglutide** (Ozempic®)#

Incretins are *responsible for* 60-70% of *postprandial* **Insulin** *secretion*;
- **Glucagon-like Peptide-1** (**GLP-1**) & **Gastric Inhibitory Peptide** [or Glucose-dependent Insulinotropic Peptide] (**GIP**) are **Incretins** and **released** *after* **eating** → ↑ **Insulin** and ↓ **Glucagon** *secretion*, *slow* **gastric emptying** *time*, *reduce* **food intake** by *enhancing* **satiety** (a feeling of fullness) and *promote* **β-cell** *proliferation*.
- **Incretins** is *rapidly* **degraded** *by* **Dipeptidyl Peptidase 4** (**DPP-4**) **enzyme**.

Injectable **Incretin Mimetics** (or **Glucagon-like Peptide-1 Agonists**) are used for the *treatment* of **Type 2 Diabetes**.

Liraglutide (Saxenda®); *approved for* **Obesity**; **BMI** of ≥ **30** or ≥**27**.

Doses;
- **Exenatide** (Byetta®); **SC injectable solution**; 5 µg/dose & 10 µg/dose SC pen;
  - *Dose*; 5 µg *twice* a day for 30 days may *increase to* 10 µg *twice* a day; *within* 1 hour *before* morning and evening meal.
- **Exenatide** (Bydureon®); **SC injectable suspension**; 2mg/vial or 2mg/Pen;
  - *Dose*; 2 mg SC *once* weekly.
- **Liraglutide** (Victoza®); 18mg/3mL **SC injectable pen**; delivers doses of 0.6mg, 1.2mg, or 1.8 mg; approved *for* **Type 2 Diabetes**;
  - *Dose*; 0.6 mg once daily for one week (only to decrease GI side effects and does not provide glycemic control) then increase to 1.2 mg once daily (If glycemic control not achieved, can increase to 1.8 mg once daily).
- **Liraglutide** (Saxenda®);18mg/3mL **SC injectable pen**; delivers doses of 0.6mg, 1.2mg, 1.8mg, 2.4mg or 3 mg; approved *for* **Obesity**;
  - *Dose*; 0.6 mg once daily for one week; increase by 0.6 mg daily at weekly intervals to a target dose of 3 mg once daily.

- **Lixisenatide** (**Lyxumia**®; Europe) (**Adlyxin**®; US);
  - 50mcg/mL in 3mL **SC injectable pen** (green pen); initial dose pen.
  - 100mcg/mL in 3 mL **SC injectable pen** (burgundy pen); Maintenance.
  - ***Dose***; 10 mcg SC once daily for 14 days, Increase dose to 20 mcg SC once daily starting on Day 15.
- **Albiglutide** (**Tanzeum**®); 30mg/pen or 50mg/pen (single-use injectable pen).
  - ***Dose***; 30 mg SC once weekly; may increase to 50 mg once weekly if glycemic response is inadequate.
- **Dulaglutide** (**Trulicity**®); 0.75mg/0.5mL pen or 1.5mg/0.5mL (single-use).
  - ***Dose***; 0.75 mg SC once weekly, may increase dose to 1.5 mg once weekly for additional glycemic control.
- **Semaglutide** (**Ozempic**®); 1.34mg/mL; delivers doses of 0.25mg, 0.5mg, or 1mg
  - ***Dose***; 0.25 mg SC once weekly for 4 weeks initially; THEN increase the dosage to 0.5 mg once weekly, If glycemic control not achieved after at least 4 weeks on 0.5-mg dose, can increase to 1 mg once weekly.

Common **Side Effects**; **Injection-site nodule** and **reactions, nausea, vomiting & diarrhea.**

 # # Black Box Warning; ***Increased*** *incidence of* **Medullary Thyroid Carcinoma (MTC)** [**C-cell** or **Parafollicular** ***tumors***] ***serum*** **Calcitonin** or **thyroid ultrasound** ***monitoring*** *are needed.*

Increased **risk** of **pancreatitis** (***unexplained*** ***persistent*** ***severe*** **abdominal pain**); *due to* **proliferative effects** in the **pancreas.**

2) Dipeptidyl Peptidase-4 (DPP-4) inhibitors "Gliptins"

Sitagliptin (Januvia®)#	**Vildagliptin** (Galvus®)#	**Saxagliptin** (Onglyza®)#
Linagliptin (Tradjenta®)#	**Alogliptin** (Nesina®)#	**Gemigliptin** (Zemiglo®)
Anagliptin (Suiny®)	**Teneligliptin** (Tenelia®)	**Trelagliptin** (Nesina®)
Omarigliptin (Marizev®)	**Evogliptin** (Suganon®)	**Gosogliptin** (SatRx®)

Sitagliptin, **Saxagliptin**, **Linagliptin**, **Alogliptin** are the ***only*** **DPP-4 inhibitors** *approved by* **US FDA**. **Vildagliptin** is ***approved*** in **European Union (EU)**.

- **Gemigliptin** (approved in Korea), **Anagliptin** (approved in Japan), **Teneligliptin** (approved in Japan), **Trelagliptin** (approved in Japan), **Omarigliptin** (approved in Japan; once-weekly), **Evogliptin** (approved in South Korea) and **Gosogliptin** (approved for use in Russia).

DPP-4 ***inhibitors*** used in **Type 2 Diabetes** as ***monotherapy*** or in ***combination*** with **Metformin**, **Thiazolidinediones** or **Sulfonylureas**.

Fixed dose combination *examples*;

- **Sitagliptin** + **Metformin** (**Janumet**® 50/500, 50/850, 50/1000 mg); ***twice*** **daily** *with* **meals**.
- **Sitagliptin** + **Metformin XR** (**Janumet**® **XR** 50/500, 50/1000, 100/1000 mg); ***once*** **daily** *with* **meals**.
- **Vildagliptin** + **Metformin** (**Galvus**® **Met** 50/500, 50/850, 50/1000 mg); ***twice*** **daily** *with* **meals**.
- **Saxagliptin** + **Metformin XR** (**Kombiglyze**® **XR** 2.5/1000, 5/1000 mg); ***once*** **daily**.
- **Linagliptin** + **Metformin** (**Jentadueto**® 2.5/500, 2.5/850, 2.5/1000 mg); ***twice*** **daily**.
- **Linagliptin** + **Metformin XR** (**Jentadueto**® **XR** 2.5/1000, 5/1000); ***once*** **daily**.

Common **Side Effects**; *In general*; **DPP-4 inhibitors** are ***well tolerated***, with the ***most common*** **side effects** are **Nasopharyngitis**, **headache**, **nausea** and **hypersensitivity reactions**.

 # Post-marketing Reports and Warning;

- ***Risk*** of **acute pancreatitis** (**fatal** and **nonfatal**) and ***severe*** **allergic** and **hypersensitivity reactions** (especially with **Sitagliptin**)
- ***Risk*** of ***severe*** and ***disabling*** **joint pain** (**Arthralgia**).
- **Saxagliptin** and **Alogliptin** may ***increase*** the ***risk*** of **heart failure**.
- **Vildagliptin** may cause **hepatitis** (**liver function tests** should be ***performed***).
- **Acute liver failure** *attributed to* **Alogliptin** *have been* ***reported***.

3) Injectable Amylin Analogues

Pramlintide (Symlin®)#

- **Pramlintide** is a ***synthetic*** **Amylin** ***analogue*** with ***substitutions*** of **Proline** at ***positions*** **25, 28** and **29**. These modifications make **Pramlintide** ***soluble***, ***non-self*****-aggregating** and *suitable for* **pharmacologic use**.

Pramlintide is **used** as an ***adjunct*** to **Insulin** ***therapy*** in *patients with* **Type 1** and **Type 2**.

Pramlintide is ***administered*** by **SC injection** ***immediately*** **prior** to **meals**;

When **Pramlintide** is ***initiated***, the ***dose*** of **postprandial** ***short-acting*** **Insulin** ***should be decreased by*** **50%** to ***avoid*** a ***risk*** of ***severe*** **hypoglycemia**.

- ***Dose range*** (***should be*** **initiated**); - 15 to 60 mcg SC for type 1 patients.
  - 60 to 120 mcg SC for type 2 patients.

Pramlintide ***should*** be **injected** by **itself** ***using*** a ***separate*** **syringe**; it ***cannot*** be ***mixed*** *with* **Insulin**.

Common **Side Effects**; **hypoglycemia**, **nausea**, **vomiting** and **anorexia**.

- **Contraindications**; **Hypersensitivity**, **Gastroparesis** and **Hypoglycemia** ***unawareness***.

V) Glycosurics

Sodium/Glucose Co-transporter-2 (SGLT2) Inhibitors "Gliflozins"

Dapagliflozin (Forxiga®) (Farxiga®)#	**Canagliflozin** (Invokana®)#
Empagliflozin (Jardiance®)#	**Ertugliflozin** (Steglatro®)
Ipragliflozin (Suglat®)	**Tofogliflozin** (Apleway®)

Dapagliflozin is the ***first*** **SGLT2 inhibitor** *approved in* **2011** by the **EU** (Forxiga®; for-SEE-ga) and in **2014** by **US FDA** (Farxiga®; far-SEE-ga).

Canagliflozin is the ***first*** **SGLT2 inhibitor** *approved by* **US FDA** in **2013**.

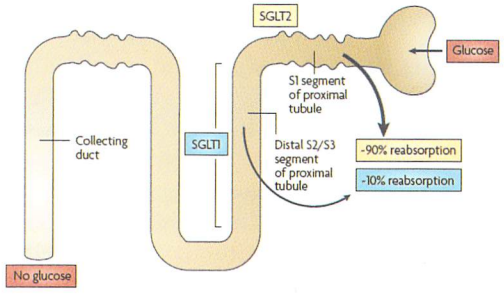
Empagliflozin is the ***third*** **SGLT2 inhibitor** *approved by* **US FDA** in **2014**.

Ertugliflozin is the ***fourth*** **SGLT2 Inhibitor** *approved in* the **US FDA** on December 19, **2017**.

- **Ipragliflozin** and **Tofogliflozin** are *approved in* **Japan**.

- **Sotagliflozin**, a ***dual*** **SGLT1/SGLT2 inhibitor**, in **phase III trials**, *under* development by Lexicon.

They are ***inhibits*** **SGLT2**, which is ***responsible for*** at least **90%** of the **glucose** ***reabsorption*** in the **kidney**, ***blocking*** this **transporter** causes **blood glucose** to be ***eliminated*** *through the* **urine → Glycosuria**.



Uses;

- As an ***adjunct*** to **diet** and **exercise** to ***improve*** **glycemic control** in **adults** with **Type 2 Diabetes**.
- **Empagliflozin** also ***indicated*** to ***reduce*** the ***risk*** of **Cardiovascular Death** in **adults** with **Type 2 Diabetes** and **Cardiovascular Disease**.

SGLT2 inhibitors are given **orally** ***once*** **daily** in the ***morning***;

Canagliflozin ***should be*** used *before* the ***first*** **meal** of the **day**.

Dapagliflozin, **Empagliflozin** and **Ertugliflozin** are **used** ***with*** or ***without*** **food** in the **morning**.

Common Side Effects;
  # Renal Impairment (>10%).
  # Urinary Tract Infection and *Increased* Urination (<10%).
  # *Female* Genital Mycotic (Fungal) Infections (<10% with Dapagliflozin, and Empagliflozin, while >10% with Canagliflozin and Ertugliflozin).
  # *Others*; - *Male* Genital Mycotic Infections, Nausea and Constipation.
    - Dyslipidemia with Dapagliflozin and Empagliflozin.
    - In 2015, the US FDA issued a *warning* that the SGLT2 inhibitors may *lead to* Ketoacidosis.
    - In 2016, a report show the Canagliflozin may ↑ *risk* of bone fracture.
    - In 2017, the FDA *concluded* (Boxed Warning) that Canagliflozin causes an *increased risk* of leg and foot amputations.

Contraindications;
  # Hypersensitivity to the drug or *any* component of the formulation.
  # *Severe* Renal Impairment, End-stage Renal Disease (ESRD) or Patients on Dialysis;
    - Canagliflozin and Empagliflozin are *contraindicated* in patients with estimated GFR *less than* 45 mL/min/1.73 m².
    - Dapagliflozin and Ertugliflozin are *not recommended* for use in patients with estimated GFR *less than* 60 mL/min/1.73 m².
    - Dapagliflozin and Ertugliflozin are *contraindicated* in *persistent* GFR 30-60 mL/min/1.73 m² or GFR *less than* 30 mL/min/1.73 m².

VI) Alpha-glucosidase Inhibitors

Acarbose (Glucobay®)# | **Miglitol** (Glyset®) | **Voglibose** (Voglib®)

Acarbose and Miglitol are *available* in the United States, while Voglibose is *available* in Japan, Korea and India.
The α-glucosidase inhibitors *competitively* inhibit the *intestinal* α-glucosidase enzymes, *delaying* the digestion and absorption of starch and disaccharides, *resulting* in *lower* postprandial glucose.
Common Side Effects; flatulence, diarrhea and abdominal pain.
Contraindications; Patients with inflammatory bowel disease, colonic ulceration or intestinal obstruction.
Hypoglycemia *should be treated* with Glucose (*not* Sucrose; *breakdown* may be blocked).

VII) Others

1) Bile Acid Sequestrant

Colesevelam (WelChol®)#

Colesevelam is bile acid sequestrant and cholesterol-lowering drug, is used in Type 2 Diabetes who are *not* achieved *adequate* control *with* medications, diet and exercise.
- The *exact* mechanism of action is *unknown*, but involve in *decrease* Farensoid X receptor (FXR) activation, FXR is a nuclear receptor with effect on cholesterol and glucose metabolism.

2) Dopamine Agonist

Bromocriptine (Cycloset®)#

Quick-release *formulation* of Bromocriptine (Cycloset®) given once in the morning, is believed to *reset* the circadian clock as in a winter rhythm; ↑ *dopaminergic* neuron activity in morning *lead to* ↑ glucose tolerance.

Gonadal Hormones

Androgens

Androgens are a ***group*** of **steroids** that have **anabolic** and/or **masculinizing effects** in ***both*** **males** and **females**.
Androgens are ***synthesized*** in the **testes**, the **ovaries** and the **adrenal glands**;
- Males produce 20 times more testosterone than Females.
- Females are also more sensitive to the hormone.

The ***most*** **important androgen** *secreted by* the **testes** is **Testosterone**;
The **testes** also ***secretes*** **small amounts** of;
- ***Potent*** **androgen**; **Dihydrotestosterone** (**DHT**).
- ***Weak*** **androgens**; **Androstenedione** and **Dehydroepiandrosterone** (**DHEA**).

Androstenedione, **Dehydroepiandrosterone** (**DHEA**) and **Dehydroepiandrosterone Sulfate** (**DHEAS**) are **largely** ***produced*** in the **adrenal gland** ***rather than*** in the **testes**.
DHEA ***supplements*** may help people with; depression, obesity, lupus, and adrenal insufficiency.
DHEA ***supplements*** may also improve skin in older people and help treat osteoporosis, vaginal atrophy, erectile dysfunction and some psychological conditions.

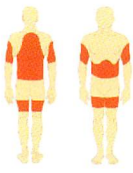
Androgenic/Anabolic Steroid (AAS) Preparations

Testosterone (AndroGel®) (Androderm®)	**Testosterone Undecanoate** (Andriol®)
Testosterone Propionate (Testoviron®)	**Testosterone Cypionate** (Depo-Testosterone®)
Testosterone Enanthate (Cidotestone®) (Delatestryl®)	**Methyltestosterone** (Testred®)
Fluoxymesterone (Halotestin®)	**Oxymetholone** (Anadrol®)	**Oxandrolone** (Oxandrin®)
Metenolone (Primobolan®)	**Methandienone** (Dianabol®)	**Stanozolol** (Winstrol®)
Mesterolone (Proviron®) (Cidoviron®)	**Nandrolone Decanoate** (Deca-Durabolin®)

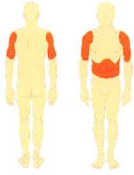
Anabolic–androgenic Steroids (**AAS**) are ***steroidal*** **androgens** that *include* ***natural*** or ***synthetic*** **androgens** that are **structurally** ***related*** and have ***similar*** **effects** to **Testosterone**.
Orally **administration** of **Testosterone** is ***rapidly*** **absorbed**, *but* it is ***largely*** *converted to* ***inactive*** **metabolites**; ***Alkylation*** of **Testosterone** at the **17α position** *such as* **Methyltestosterone**, **Fluoxymesterone** and **Oxymetholone** *allows* ***oral*** **administration** of the **hormone**.
Androgenic-*to*-anabolic Ratio;

- **Testosterone**; 1:1
- **Testosterone Cypionate**; 1:1
- **Testosterone Enanthate**; 1:1
- **Methyltestosterone**; 1:1
- **Oxymetholone**; 1:3
- **Fluoxymesterone**; 1:2
- **Oxandrolone**; 1:3 to 1:13
- **Nandrolone Decanoate**; 1:2.5 to 1:4

Routes of ***administration***;
- **Oral**; *such as* **Methyltestosterone**, **Fluoxymesterone**, **Oxymetholone**, **Mesterolone** and **Oxandrolone**.
- **IM Injections**; *such as* **Testosterone** ***esters*** (**Enanthate**, **Undecanoate**, or **Cypionate**) & **Nandrolone Decanoate**.
- **Creams/Gels** or **Skin Patches**; **Testosterone**;
  ##DO NOT APPLY TO THE SCROTUM (application sites)→
  # # # Scrotal skin is ~ 5 times more permeable to testosterone.



Testosterone patches (Androderm®)



Testosterone gel (AndroGel®)

Uses;

A) Androgenic;

- **Androgen Replacement Therapy**; *Only* for men with low levels of testosterone.
- ***Induction*** of **Male Puberty**; increase height, weight & fat-free mass in boys with delayed puberty.
- **Masculinizing Hormone Therapy**; induce masculine secondary sexual characteristics in transgender

B) Anabolic;

- **Bone Marrow Stimulation**: *especially* **aplastic anemia**; largely replaced by erythropoietin.
- **Growth stimulation**: especially people with chronic wasting conditions such as cancer and AIDS.
- **Osteoporosis** in **postmenopausal women**; Nandrolone Decanoate is approved for this use.
- **Aging males**; increase in lean body mass and a decrease in bone turnover.

C) Ergogenic [illicit use] (abuse in sports); large doses of testosterone—when given alone—or its derivatives suppress the secretion of gonadotropins and result in some atrophy in testes.

D) Others; **Breast Cancer** and **Postmenopausal** and **Transgender Women**.

Side Effects;

Male-*specific*; **Priapism, gynecomastia, azoospermia, testicular *atrophy*, prostate hypertrophy** and **prostate cancer**.

Female-*specific*: **Masculinization, voice deepening, hirsutism, menstrual *disturbances*, clitoral *enlargement*, breast atrophy** and **uterine atrophy**.

- **Testosterone *should not*** be **used** by **pregnant women**; **virilization** of the **female fetus**.

Child-*specific*: **precocious puberty** in ***boys*** and **delayed puberty** in ***girls***.

General; - *Dermatological*; **oily skin, acne, hypertrichosis, alopecia** and **fluid retention**.

- *Endocrine*: **libido *changes*, infertility** and **hypogonadism**.
- *Hepatic*: **hepatotoxicity**; ***exclusively*** *with* **17α-alkylated AAS**.
- *Cardiovascular*: **dyslipidemia, atherosclerosis, hypertension, thrombosis, myocardial infarction** and ***sudden*** **death**.
- *Psychiatric*; **mood *swings*, anxiety** and **cognitive *impairment***.

Antiandrogens

Androgen Receptor (AR) Antagonists

Flutamide (Eulexin®)	**Nilutamide** (Nilandron®)	**Bicalutamide** (Casodex®)#
Enzalutamide (Xtandi®)	**Apalutamide** (Erleada®)	

They are ***used*** for the **treatment** *of* **Prostate Cancer**.

Cyproterone Acetate (Androcur®)# (Diane® 35)#

Cyproterone acetate (**Androcur®**) or ***with*** **Ethinylestraidol** (**Diane® 35**), is an ***antiandrogen*** with ***progestational effect***, which is ***used*** in the ***treatment*** of **androgen-dependent conditions** *like* **acne, seborrhea, hirsutism, early puberty, prostate cancer** and in **birth control**.

Spironolactone (Aldactone®)#

Spironolactone is a ***synthetic*** **steroid** that *acts as* a **competitive antagonist** at **mineralocorticoid receptors** and **androgen receptors**, which is ***used*** in the ***treatment*** of **androgen-dependent conditions**; **hirsutism, acne** in ***women*** and **androgenic alopecia**.

Androgen Synthesis Inhibitors

Ketoconazole	**Abiraterone** (Zytiga®)#

- **Ketoconazole** is an **antifungal** and ***older*** **17α-hydroxylase *inhibitor***.

Abiraterone is a ***new*** **17α-hydroxylase *inhibitor***, ***used*** in **Prostate Cancer**.

Finasteride (Proscar®)#	**Dutasteride** (Avodart®)#	**Alfatradiol** (Pantostin®)

Finasteride and **Dutasteride** are **5α-reductase *inhibitors***, they are ***used*** in **Benign Prostatic Hyperplasia (BPH)**. **Finasteride** is ***also*** **used** in **Androgenic Alopecia** and **Hirsutism**.

Alfatradiol is ***another*** ***5α-reductase inhibitor*** **used** ***topically*** in **Androgenic Alopecia**.

Estrogens

The ***major*** **Estrogens** *produced by* **women** are **Estrone** (E_1), **Estradiol** (E_2) and **Estriol** (E_3). ***Another type*** called **Estetrol** (E_4) is *produced* ***only*** *during* **pregnancy**.
Estradiol (E_2) is the ***major*** **secretory** ***product*** of the **ovary**.
Estradiol (E_2) is the ***strongest***, *whereas* **Estriol** (E_3) is the ***weakest***.
Estrogens, in females, are ***produced*** *primarily* by the **ovaries** and **placenta** (during pregnancy) *under the* ***effect*** of **FSH**.
Some **Estrogens** are also **produced** in ***smaller amounts*** by **other tissues** *such as* **liver**, **adrenal glands**, **adipose tissue** and **breasts**.

Estrone (E_1)	Estradiol (E_2)	Estriol (E_3)	Estetrol (E_4)

Estradiol (**17β-estradiol**) is the ***most potent*** **estrogen** *produced* and *secreted by* the **ovary**. It is the ***principal*** **estrogen** in **premenopausal women**.
Estrone and **Estriol** are a ***metabolite*** of **Estradiol**
Estrone is the ***primary*** *circulating* **estrogen** ***after*** **menopause** and it is ***generated*** *mainly* from *conversion of* **Androstenedione** in ***peripheral*** **tissues**.

Estrogen Preparations

Natural Estrogens

Micronized Estradiol (Estrace®)#	**Estradiol** *Transdermal* (Estraderm®)#
Estradiol Benzoate (Agofollin®)	**Estradiol Cypionate** (Depo-Estradiol®)
Estradiol Valerate (Delestrogen®)	**Conjugated Estrogens** (Premarin®)#
Estradiol Hemihydrate (Fem 7®)#	

- **Estradiol** **orally** is ***rapidly*** **metabolized** (and partially inactivated) by **liver** ***microsomal*** **enzymes**.
- ***Micronized*** **Estradiol** **tablets** (and vaginal cream) is ***available*** and has ***better*** **bioavailability** and can be taken ***sublingually*** *instead of* **orally**.
- ***Transdermal*** **Estradiol** is *available* in forms of **topical gels**, **patches**, **sprays** and **emulsions**.
- **Ester** ***prodrug*** of **Estradiol** such as **Estradiol Benzoate**, **Estradiol Cypionate** and **Estradiol Valerate** can be administered by **IM injection**, which a **long-lasting** ***depot*** **effect** ***occurs***.
- **SC implant Estradiol** (**Encore**®) is alos *available*.
- **Conjugated Estrogens** (**Premarin**®) (**Pregnant mare's urine**); is a ***mixture*** of the **sodium salts** of **estrogen conjugates**, such as **Estrone Sulfate** and **Equilin Sulfate** *obtained from* **urine** of **pregnant mares**. It is available in **oral**, **IV**, **IM**, and **topical** ***preparations***.
- **Estradiol Hemihydrate** is ***more*** **hydrated** (***more*** **insoluble** in **water**), which results in ***slower*** **absorption** *rates* with *specific formulations* such as **patch** (**Fem 7**®).

Synthetic Estrogens (Steroidal)

Ethinyl Estradiol	**Mestranol**	**Quinestrol**

Synthetic Estrogens (Non-Steroidal)

Diethylstilbestrol	**Chlorotrianisene**	**Methallenestril**

- **Ethinyl Estradiol** is the ***most*** **effective** **oral** **Estrogens** at ***lower*** **doses** (less first-pass metabolism).
- **Mestranol** is a ***prodrug*** of **Ethinyl Estradiol** formulated in ***combination*** *with* a **Progestin** in **birth control pill** (not available alone);
  - It was the estrogen component in the first birth control pill, such as mestranol/noretynodrel (Enovid®).
  - In 1969, mestranol was replaced by Ethinylestraidol in most birth control pills.
- **Quinestrol** is a ***prodrug*** of **Ethinyl Estradiol** (ethinylestradiol 3-cyclopentyl ether).
- **Diethylstilbestrol**, **Chlorotrianisene** & **Methallenestril** are ***synthetic*** **nonsteroidal** **estrogen**.

Uses;
- **Hormone Replacement Therapy**;
  - Menopausal symptoms (Hot flashes, vaginal atrophy and osteoporosis).
  - Under developed female secondary sex characters (Hypogonadism).
  - Transgender women (feminizing hormone therapy).
- **Birth control**; alone or in combination with progesterone as contraceptives.
- **Prostate cancer**; by suppressing testosterone levels.
- **Breast cancer**; High-dose estrogen therapy (rarely used; tamoxifen is preferred).
- ***Others***; - Suppress lactation.
  - Girls with constitutional tall stature.
  - Estrogen replacement therapy may improve Schizophrenia and Alzheimer's symptoms in women.

Side Effects;
Most Common; **Nausea, headache & breast tenderness (fluid retention)**.
Uterine bleeding (to avoid; use smallest amount of estrogen possible).
***Risk of* thromboembolic events** and **myocardial infarction**.
***Risk of* breast** and **endometrial cancer**;
Should not be **used** in *patients with* **estrogen-dependent neoplasms**.

Selective Estrogen Receptor Modulators (SERMs)

Selective estrogen receptor modulators (SERMs) are a **class of drugs** that *act on* the **estrogen receptor**, *produce* **estrogenic** and **anti-estrogenic effects *depending on*** the **specific tissue (mixed estrogen agonist/antagonist; EAA)**.
SERMs provide the ***beneficial effects*** of **Estrogen *without*** the **potentially adverse *outcomes***.
SERMs are ***used dependent*** on their **pattern of action** in **various tissues**:

SERMs	Generation	Uses	Estrogen Receptor; Location
Clomiphene	First	Ovulation Induction	***Antagonist***; hypothalamus.
Tamoxifen Toremifene	First	Breast Cancer	***Agonist***; bone and uterus. ***Antagonist***; breast.
Raloxifene	Second	Osteoporosis - Breast Cancer	***Agonist (full)***; bone. ***Antagonist***; breast and uterus.
Ormeloxifene	Third	Contraception (Only in India)	***Agonist***; bone. ***Antagonist***; breast and uterus.
Lasofoxifene	Third	Osteoporosis - Breast Cancer - Vaginal Atrophy (Only in Lithuania and Portugal)	***Agonist***; bone ***Antagonist***; breast and uterus.
Ospemifene	Third	Vaginal Atrophy - Dyspareunia	***Agonist***; bone ***Antagonist***; breast and uterus.
Bazedoxifene	Third	Osteoporosis (Combined with conjugated estrogens)	***Agonist (full)***; bone. ***Antagonist***; breast and uterus.
Arzoxifene	Third	Osteoporosis (*clinical phases*)	***Agonist (full)***; bone. ***Antagonist***; breast and uterus.

Clomiphene (Clomid®)#

Clomiphene is **used** to ***induce* ovulation** in **infertility** in **women**.
- It is *act by* ***increase*** **production** of **gonadotropins (FSH & LH)** by ***inhibiting* negative feedback** of **estrogen** on the **hypothalamus (*block* estrogen receptor** in **hypothalamus)**.

Dose;
1 tab. (50 mg) ***daily for* 5 days**, ***should be* started *on*** or ***about*** the **5th day** of **woman's cycle**.
If no ovulation → *given* **100 mg *daily for* 5 days** *at the* ***next*** **cycle**.
Side effects; *Reversible* **ovarian enlargement** and **vasomotor flushing** (>10%).
Warning; ***Risk of* ovarian enlargement & ovarian hyperstimulation syndrome**.
Use of **Clomiphene increases** the **risk** of **multiple births (twins** or **triplets)**.

Raloxifene (Evista®)#

Raloxifene is a **SERM** ***approved for*** the ***prevention*** and ***treatment*** of **osteoporosis in postmenopausal women**. It has ***estrogen-like effects*** on **bone** & ***estrogen antagonist effects*** on **breast** & **endometrium**.
It is ***FDA-approved*** for ***reduction*** in **risk** of **invasive breast cancer**.
Raloxifene causes some ***positive*** **lipid effects**.
Dose; **60 mg orally** ***once*** a **day**.
Common side effects; **hot flashes** and **leg cramps**.
FDA Black Box Warning; ***risk*** of ***venous thromboembolism*** and **death** *due to* **stroke**.
Contradictions; **lactating women** or **pregnant women** (**Category X**) and in **women** with ***active*** or ***past history*** of **venous thromboembolic events**.

Tamoxifen (Nolvadex®)# | Toremifene (Fareston®)

Tamoxifen and **Toremifene** have ***estrogenic effects*** in **bone** and **uterus** and ***estrogen antagonist effects*** on **breast**.
Tamoxifen is ***taken orally*** *daily* for **5 years** for **breast cancer**.
Off-label use of **Tamoxifen**;
    # **Ovulation induction**; **5-40 mg** ***every*** **12 hrs** for **4 days**; **3rd-7th** of **cycle**.
- **Tamoxifen** is ***metabolized*** by the **CYP450** (**CYP2D6** and CYP3A4) into ***active*** **metabolites**;
Tamoxifen has the ***potential*** to *cause* **Endometrial Cancer**.
Common side effects; **Hot flashes, nausea/vomiting, vaginal bleeding discharge, bone pain** and **thromboembolism**.
Fulvestrant (**Faslodex®**) is a ***selective*** **Estrogen Receptor Degrader** (**SERD**), it **works** by ***binding*** to the **estrogen receptor** and ***destabilizing*** **it**, and ***downregulates*** **estrogen receptors** and ***inhibits*** **breast tumor** ***growth.*** It is ***given*** **IM** for **Hormone Receptor–Positive** ***advanced*** **Breast Cancer**.

Progestins

Progesterone

Progesterone is the ***most important*** **progestin** in **humans**.
Progesterone ***serves*** as a ***precursor*** to the **Estrogens**, **Androgens** and **Adrenocortical Steroids**.
It is ***synthesized*** in the **ovary** (corpus luteum), **placenta** (***large*** **amounts** *during* **pregnancy**), **testis** and **adrenal cortex** in ***response to*** **LH**.
Function;
- **Uterus**;
    - *Helps* ***implantation*** and ***formation*** of **placenta**.
    - ***Maintains*** **pregnancy** by:
        - ***Preparing*** the **endometrium** for ***implantation***.
        - ***Inhibit*** **uterine** ***contraction***.
        - ***Decrease*** **myometrium** ***sensitivity*** to **Oxytocin**.
- **Fallopian Tube**;
    - ***Stimulate*** **mucus** ***secretion*** for ***nutrition*** of the ***fertilized*** **ovum** ***during*** its **migration**.
- **Vagina**;
    - ***Stimulate*** **thick** ***secretion***, *making it* ***thick*** and ***impenetrable*** to **sperm**.
- **Others**;
    - ***Decrease*** **Na^+ reabsorption**; by compete with aldosterone for the mineralocorticoid receptors.
    - ***Increases*** **body temperature**.

Progestin Preparations

Progesterone and Derivatives

Progesterone (Prontogest®)#	**Medroxyprogesterone** (Provera®)#
Medroxyprogesterone Acetate (Depo-Provera®)#	
Hydroxyprogesterone Caproate (Proluton®)	**Megestrol Acetate** (Megace®)

Medroxyprogesterone Acetate ***injections*** is **used** ***once*** *every* **3 months** as **birth control** and in **endometriosis**.

Hydroxyprogesterone Caproate is **used** ***once*** **weekly** to ***prevent*** **preterm birth** in **pregnant**.

Megestrol Acetate is **used** ***mainly*** as an **appetite stimulant** to treat **wasting syndromes** and *also* **used** in the treatment of ***advanced*** **breast cancer** and **endometrial cancer**.

First Generation Progestins

Norethisterone (Primolut® N)#	**Norethisterone Acetate** (Primolut-Nor®)#
Norethynodrel (Enovid®)	**Lynestrenol** (Exluton®)
Ethynodiol Diacetate (Demulen®)	

These compounds *known as* **19-Nortestosterone** ***derivatives***.

Norethindrone or **Norethisterone** was the ***first*** **orally** *highly active* **progestin**.

Norethisterone and **Lynestrenol**; ***Low*** **progestational** ***activity***, ***slight*** **estrogenic** ***activity*** & ***more*** **androgenic** ***activity***.

Ethynodiol Diacetate; ***Medium*** **progestational** ***activity***, it has ***minor*** **estrogenic effects** and ***little*** **androgenic** ***activity***.

Second Generation Progestins

Norgestrel (Ovral®)#	**Levonorgestrel** (Microlut®)#

Norgestrel is a ***mixture*** of both **Dextronorgestrel** (***inactive***) and **Levonorgestrel** (***active***).

Norgestrel is a **19-Nortestosterone** ***derivatives***.

Levonorgestrel is the ***most*** **widely prescribed** contraceptive **progestin** *worldwide*.

It has ***high*** **progestational** and **androgenic effects**.

It is ***Used in*** **birth control** has also been ***FDA approved*** for **emergency contraception**.

Third Generation Progestins

Desogestrel (Cerazette®)#	**Norgestimate** (Cilest®)#
Gestodene (Gynera®)#	**Etonogestrel** (Nexplanon®)#

Desogestrel, **Norgestimate**, **Gestodene** and **Etonogestrel** are ***high*** **progestational** ***selectivity***, ***minimizing*** or ***no*** **androgenic** ***effects*** and **estrogenic** ***activity***.

They are ***less*** **negative** ***impact*** on **glucose** and **lipid metabolism**, **weight gain** and **acne**.

Fourth Generation Progestins

Dienogest (Visanne®)#	**Drospirenone** (Yasmin®)#
Segesterone Acetate (Nestorone®)	**Nomegestrol Acetate** (Lutenyl®)
Trimegestone (Totelle®)	**Norelgestromin** (Evra®)

Dienogest has ***high*** **progestational** ***selectivity*** with ***some*** **antiandrogenic** ***activity***, which may help to ***improve*** **androgen-dependent symptoms** *like* **acne**.

Drospirenone has ***high*** **progestational** ***selectivity*** with **antimineralocorticoid** ***effects***, leading to ***decreased*** **salt** and **water retention** *caused by* the **estrogen** in **birth control pills**.

- **Segesterone Acetate** *available* ***only*** as **implant**.
- **Nomegestrol Acetate** and **Norelgestromin** has ***some*** **antiandrogenic** ***activity***.
- **Trimegestone** has ***weak*** **antiandrogenic** and **antimineralocorticoid** ***activity***.

Uses;
- **Birth control**;
  - Alone or in combination with Estrogen as contraceptives.
  - Stimulate thick secretion, making it thick and impenetrable to sperm.
- **Hormone Replacement Therapy**;
  - Progestins are commonly used as a component of menopausal hormone therapy in women to prevent endometrial hyperplasia and increased risk of endometrial cancer from unopposed estrogen therapy.
  - Also used in transgender hormone therapy.
- **Support pregnancy**;
  - Prevent recurrent pregnancy loss.
  - It is used for luteal support in in-vitro fertilization protocols.
- **Dysfunctional uterine bleeding** and **Endometriosis**.
- **Endometrial Cancer** and **Breast Cancer**;
  - Megestrol acetate and medroxyprogesterone acetate are effective.
- **Appetite Stimulation**;
  - Megestrol acetate are effective and medroxyprogesterone acetate is also used.

Side Effects;
Most Common; **headache**, **depression**, **weight gain** and ***changes*** in **libido**.
19-nortestosterone Progestins *such as* **Norethindrone** & **Levonorgestrel**; *possess* ***some*** **androgenic activity** (structural similarity to testosterone) and *can* **cause acne** and **hirsutism**.
Drospirenone *may* **cause hyperkalemia** due to **antimineralocorticoid** ***effects***.

FDA Warning;
Estrogen plus **Progestin** *substudy reported* an ***increased*** **risk** of **deep vein thrombosis (DVT)**, **pulmonary embolism (PE)**, **stroke** and **myocardial infarction (MI)** in **postmenopausal women**.
Estrogen plus **Progestin** *substudy demonstrated* an ***increased*** **risk** of ***invasive*** **breast cancer**.
The **FDA** ***recommends*** that **Medroxyprogesterone Acetate** by ***injection not*** be **used** for ***longer than*** **2 years**, due to *concerns* ***over*** **bone loss**.

Selective Progesterone Receptor Modulators (SPRM)

Mifepristone (Mifeprex®)#

Mifepristone is a **Progesterone** **receptor** ***antagonist*** and ***partial*** **agonist** **activity** (in the absence of progesterone, mifepristone acts as a partial agonist) with ***powerful*** **glucocorticoid** **receptor** ***antagonist*** **effect**.

Uses;
- ***Medical*** **abortion** (usually ***combined with*** **Misoprostol**); first- & second-trimester medical abortion.
- **Emergency contraceptive**.
- **Cushing's syndrome** (treatment of **hyperglycemia**).

Most common side effects; **Abdominal pain**, **cramping**, **nausea/vomiting**, **headache** and **vaginal spotting**.

Ulipristal Acetate (Ella®)

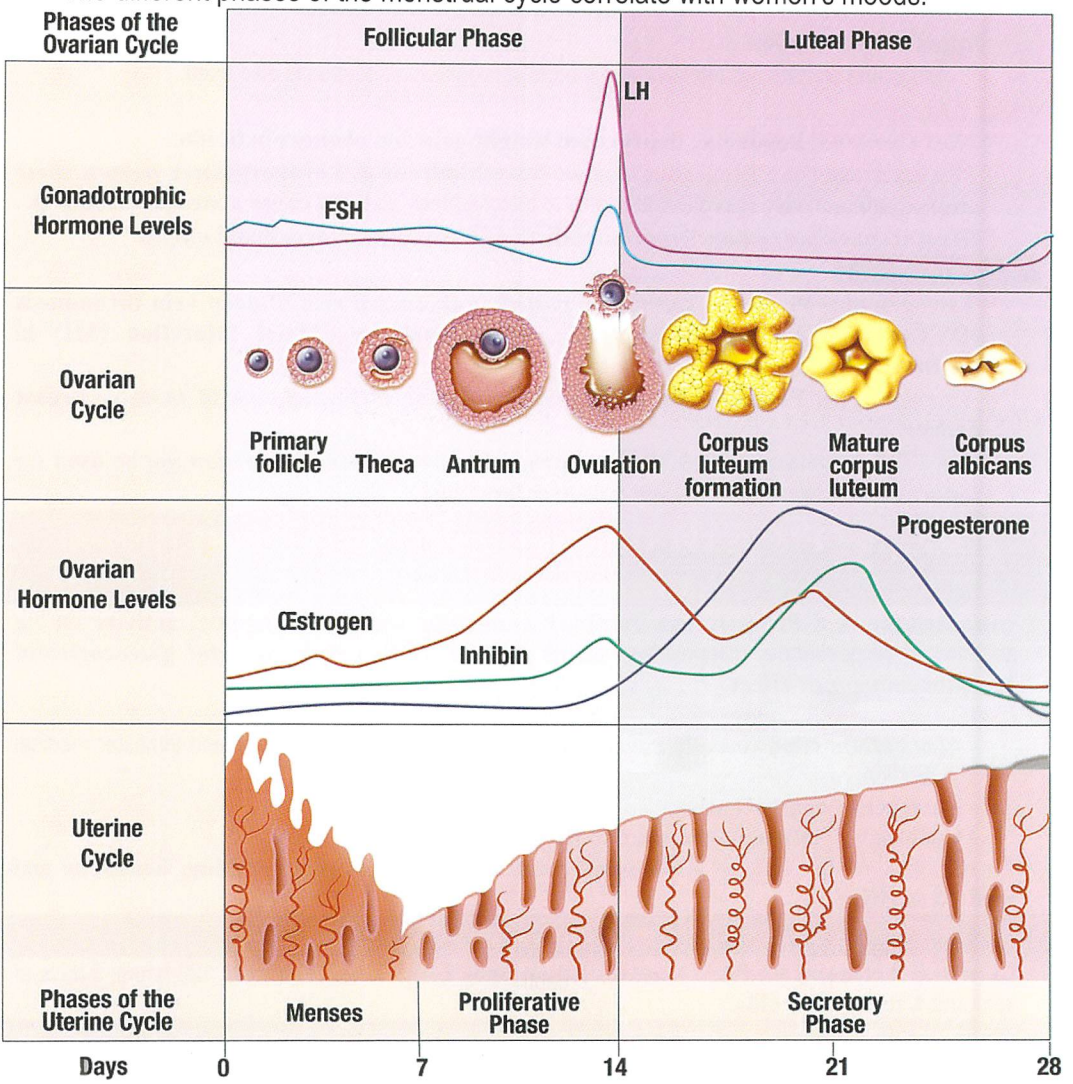
Ulipristal Acetate is a **SPRM** ***used*** for **Emergency Contraceptive** (within 120 hours; 5 days of sex) and **Uterine Fibroids**.

Vilaprisan	**Asoprisnil**	**Telapristone**

- **Vilaprisan**, **Asoprisnil** and **Telapristone** are **SPRM** ***under*** **development**.

Contraceptive Methods

- **Menstrual Cycle**;
  - The menstrual cycle is the regular natural change that occurs in the female reproductive system that makes pregnancy possible.
  - The cycle is required for the production of oocytes, and for the preparation of the uterus for pregnancy.
  - Menstruation stops occurring after menopause which usually occurs between 45 and 55 years of age.
  - The average menstrual cycle lasts 28 days.
  - The variability of menstrual cycle lengths is highest for women under 25 years of age and is lowest that is, most regular, for ages 25 to 39.
  - The different phases of the menstrual cycle correlate with women's moods.



A) Ovarian Cycle;

1) Follicular Phase;

- The body prepares itself to accept and support a pregnancy.
- The endometrium (lining of the uterus) grows and thickens, and the vaginal environment also changes in order to become more sperm friendly.
- During this phase; increase secretion of FSH during the first days of the cycle to stimulate ovarian follicles, of which one becomes dominant before ovulation.
- The follicle that reaches maturity is called a Graafian and it contains the ovum.
- Two hormones dominating the follicular phase are FSH and Estrogen.

2) Ovulation Phase;

- Each cycle, only one egg is released from the dominant ovarian follicle in response to a surge in LH, and can only be fertilized for up to 48 hours.

3) Luteal Phase;

- During the luteal phase, corpus luteum produce high levels of progesterone and moderate levels of estrogen and inhibin.
- The hormones produced by the corpus luteum also suppress production of the FSH and LH that the corpus luteum needs to maintain itself.
- Glands in the endometrium secrete proteins in preparation for the implantation of the fertilized egg.
    - If pregnant, the embryo will implant itself in the endometrium during this phase.
    - If implantation does not occur, the endometrium starts to break down and is eventually sloughed off menstruation.
- Falling levels of progesterone trigger menstruation and the beginning of the next cycle.

B) Uterine Cycle;

1) Menses Phase;

- Regular menstruation that lasts for a few days (usually 3 to 5 days, but anywhere from 2 to 7 days is considered normal).
- The average blood loss during menstruation is 35 milliliters with 10–80 ml considered normal.
- Painful cramping in the abdomen, back, or upper thighs is common during the first few days of menstruation.
- Severe uterine pain during menstruation is known as **dysmenorrhea**, and it is most common among adolescents and younger women, Common symptoms include abdominal pain, breast tenderness and swelling, headache and back pain.
- **Premenstrual Syndrome** (**PMS**) is a combination of emotional, physical, psychological, and mood disturbances that occur in the one to two weeks before Menstruation; Common symptoms include acne, breast tenderness, bloating, feeling tired, irritability and mood changes.

2) Proliferative Phase;

- Estrogen causes the lining of the uterus to grow, or proliferate, during this time.
- The ovarian follicles secrete increasing amounts of estradiol (estrogen).
- The estrogens initiate the formation of a new layer of endometrium in the uterus, histologically identified as the proliferative endometrium.
- The estrogen also stimulates crypts in the cervix to produce fertile cervical mucus, which may be noticed by women practicing fertility awareness.

3) Secretory Phase;

- The corpus luteum produces progesterone, which plays a vital role in;
    - Making the endometrium receptive to implantation.
    - Supportive of the early pregnancy, by increase blood flow and uterine secretions and reducing the contractility of the smooth muscle in the uterus.
    - It also has the side effect of raising the woman's basal body temperature (BBT).

- ***Contraceptive Methods***:
  - I- **Hormonal contraceptives.**
  - II- **Vaginal Spermicides.**
  - III- **Barrier contraceptives.**
  - IV- **Intrauterine devices.**
  - V- **Sterilization methods.**
  - VI- **Natural Methods.**
  - VII- **Emergency contraceptives.**

Hormonal Contraceptives

I) Oral Contraceptives (Oral Pills)

A) Combination Oral Contraceptives (COCs)

Monophasic (Fixed Combination)	Biphasic Combination	Triphasic Combination
Containing a fixed ration of **Estrogen** and **Progestin** given daily for 21 days, beginning on day 5 of the menstrual cycle	Containing a fixed dose of **Estrogen** (days 1-21) Containing a different dose of **Progestin** (days 1- 10) lower than (days 11 -21)	Containing 3 different doses gradual **Estrogen** increase and/or some pills may also increase the dose of **Progestin**.
1) High dose of E & P **Primovlar®** **Ethinyl Estradiol** 0.05 mg **Norgestrel** 0.5 mg	**Necon®** **Light yellow tablet** (10 tab) **Norethindrone** 0.5 mg **Ethinyl Estradiol** 0.035 mg	**Triocept®** **6 Tablets** **Levonorgestrel** 0.05 mg **Ethinyl Estradiol** 0.03 mg
2) Low dose of E & P **Microvlar® - Microcept®** **Ethinyl Estradiol** 0.03 mg **Norgestrel** 0.15 mg	**Dark yellow tablet** (11 tab) **Norethindrone** 1 mg **Ethinyl Estradiol** 0.035 mg	**5 Tablets** **Levonorgestrel** 0.075 mg **Ethinyl Estradiol** 0.04 mg
3) Low dose of E & high dose of P **Loestrin®** **Ethinyl Estradiol** 0.03 mg **Norethisterone** 1.5 mg		**10 Tablets** **Levonorgestrel** 0.125 mg **Ethinyl Estradiol** 0.03 mg

B) The Mini-Pill (Progestin Only Pill -POP)

Microlut® - Micronor® - Exluton®

- **Progestin *only*** is given for **28 days *continuously***.
- It is ***less* effective** than **COCs**, ***especially*** if **one** or **more tablets** are ***missed***.
- ***Good choice*** in **women** are *unable to* take **Estrogen** (*due to estrogen related side effect*).

C) Sequential Method

- *Start by* **Estrogen alone** for **14-16 days**, then ***combination of* Estrogen** & **Progestin** for **5-6 days**; ***success*** about 98-99%.

D) Emergency Contraceptive (Post-Coital or Morning After Pills)

1- Progestin-only method

Levonorgestrel (Contraplan II® - 0.75 mg)#

- The pills containing ***high dose*** of **Levonorgestrel 0.75 mg**.
- This pill typically ***works up*** to **72 hours *after* intercourse** by using **2 tablets (1.5 mg)**.

2- Yuzpe Regimen

Estrogen + Progesterone

- Taken as ***two doses*** at a **12-hour interval**; large doses of ***both* Estrogen** and **Progestin**.
- Each dose can vary from 2 to 5 pills depending on the brand of medication being used.
- The ***standard regime*** is **2 tablets** each with **0.05 mg Ethinyl Estradiol** and **0.25 mg Levonorgestrel**, to be repeated 12 hours later; ***works up*** to **72 hours *after* intercourse**.

3- Selective Progesterone Receptor Modulator (SPRM)

Ulipristal Acetate (EllaOne®)# - (Ella®)#

- **Ulipristal acetate** is a ***selective progesterone receptor modulator*** **(SPRM)**.
- **Ulipristal acetate 30 mg tablet** is ***used*** **within 120 hours** (5 days) ***after*** **intercourse**.

Mifepristone (Mifeprex®)#

- **Mifepristone** is a ***selective progesterone receptor modulator*** **(SPRM)**.
- ***Used*** in **medical abortion** & **emergency contraceptive**.
- ***Now***; **Mifepristone** with **Misoprostol** ***widely used*** in **abortion**; **Do not get involved**!

2) Injection Contraceptives

Depot Medroxyprogesterone Acetate (DMPA) (Depo-Provera®)#

- **Depo-Provera®** ***contains*** **DMPA 150 mg**, a ***derivative of*** **Progesterone**.
- *Given by* **deep IM injection** *every* **3 months**.

Norethisterone Enanthate (Noricept®)#

- **Norethisterone Enanthate 200 mg**, a ***derivative of*** **Progesterone**.
- *Given by* **deep IM injection** *every* **2 months**.

Norethisterone Acetate + Estradiol Valerate (Mesigyna®)#

- ***Monthly*** **Contraceptive Injection**
- ***Contains*** **Norethisterone Acetate 50mg** + **Estradiol Valerate 5mg**.
- *Given by* **deep IM injection** *every* **1 months**.

3) Contraceptive Implants

- **Progestin** ***filled*** **rods** or **capsules** that are ***inserted*** *under* the **skin**.

First Generation (6 Rods System)

Norplant® System

- filled by **36 mg** of **Levonorgestrel**. ***Implanted*** **sub-dermally** in the **upper arm**, ***for*** **5 years**

Second Generation (2 Rods System)

Jadelle®

- Each containing **75 mg** of **Levonorgestrel**. **Sub-dermally** in the **upper arm**.
- ***Effective*** for **3 years**.

1 Rods system

Nexplanon® - Implanon®

- It is contains **68 mg** of **Etonogestrel** (Progestin). **Sub-dermally** in the **upper arm**.
- ***Effective*** for **3 years**.

4) Vaginal ring

NuvaRing®

- It is **contains** slowly releases **Estrogens** and/or **Progestins**. ***Remove*** the **ring 3 weeks** *after* **insertion** on the **same day** of the **week** it was inserted at about the ***same time*** of **day**.

5) Contraceptive Patch

Ortho Evra®

- It is a **transdermal patch** *contains* **Estrogens** and **Progestins** *applied to* the **skin** ***once*** a **week** for **3 weeks**, and then stop using for **1 weeks** (patch-free week); Like a period.

6- Hormonal Intrauterine Device

Mirena® - Skyla®

It is a small 'T'-shaped device, containing **Levonorgestrel**; ***effective up to*** **5 years.**

Miscellaneous Agents

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Cancer Chemotherapy

Anti-Cancer Drugs

Cytotoxic Drugs

I) Antimetabolites

Folic
- *Methotrexate
- *Pemetrexed (Alimta®)
- *Pralatrexate (Folotyn®)

Purine
- #6-Mercaptopurine (Purinethol®)
- #Fludarabine (Fludara®)
- #Cladribine (Leustatin®)

Pyrimidin
- *5-Fluorouracil (Adrucil®)
- *Capecitabine (Xeloda®)
- *Floxuridine (FUDR®)

Cytidine
- #Azacitidine (Vidaza®)
- #Cytarabine (Ara-C®)
- #Gemcitabine (Gemzar®)

II) Alkylating Agents

Nitrogen Mustard
- #Mechlorethamine (Mustargen®)
- #Cyclophosphamide (Cytoxan®)
- #Ifosfamide (Ifex®)
- #Chlorambucil (Leukeran®)
- #Melphalan (Alkeran®)
- #Bendamustine (Treanda®)

Nitrosoureas
- *Carmustine (BiCNU®)
- *Lomustine (CeeNu®)
- *Streptozocin (Zanosar®)

Alkyl Sulfonates
- #Busulfan (Myleran®)

Triazines
- *Procarbazine (Natulan®)
- *Dacarbazine (Dtic-Dome®)
- *Temozolomide (Temodal®)

Platinum
- #Cisplatin (Platinol®)
- #Carboplatin (Paraplatin®)
- #Oxaliplatin (Eloxatin®)

III) Cytotoxic Antibiotics

Anthracyclines
- *Daunorubicin (Cerubidine®)
- *Doxorubicin (Adriamycin®)
- *Epirubicin (Ellence®)
- *Idarubicin (Idamycin®)
- *Mitoxantrone (Novantrone®)

Others
- #Bleomycin (Blenoxane®)
- #Mitomycin (Mutamycin®)
- #Dactinomycin (Cosmegen®)

IV) Microtubule Inhibitors

Vinca Alkaloids
- Vincristine (Oncovin®)
- Vinblastine (Velban®)
- Vinorelbine (Navelbine®)

Taxanes
- Paclitaxel (Taxol®)
- Docetaxel (Taxotere®)
- Cabazitaxel (Jevtana®)

V) Endocrine Therapy

- *Prednisone (Hostacortin®)
- #Estrogens

SERM
- *Tamoxifen (Nolvadex®)
- *Fulvestrant (Faslodex®)
- *Raloxifene (Evista®)

Aromatase Inhibitors
- #Anastrozole (Arimidex®)
- #Letrozole (Femara®)
- #Exemestane (Aromasin®)
- *Megestrol Acetate (Megace®)

GnRH Analogs
- #Leuprorelin (Lupron®)
- #Goserelin (Zoladex®)
- #Triptorelin (Trelstar®)

Antiandrogens
- *Flutamide (Eulexin®)
- *Nilutamide (Anandron®)
- *Bicalutamide (Casodex®)

VI) Monoclonal Antibodies

- Rituximab (Rituxan®)
- Trastuzumab (Herceptin®)
- Pertuzumab (Perjeta®)
- Bevacizumab (Avastin®)
- Cetuximab (Erbitux®)
- Panitumumab (Vectibix®)
- *Others*

VII) Tyrosine Kinase Inhibitor

- Imatinib (Gleevec®) (Glivec®)
- Nilotinib (Tasigna®)
- Dasatinib (Sprycel®)
- Erlotinib (Tarceva®)
- Sorafenib (Nexavar®)
- Sunitinib (Sutent®)
- Lapatinib (Tykerb®)

VIII) Topoisomerase Inhibitors

*Etoposide (Toposar®) *Teniposide (Vumon®)
#Topotecan (Hycamtin®) #Irinotecan (Campto®)

IX) Non-Classified

-Interferons -L-Asparaginase (Kidrolase®)
-Abiraterone (Zytiga®)
-Enzalutamide (Xtandi®)

I) Antimetabolites

Antimetabolite is a ***substances*** **structurally similar** to ***normal*** **compounds** that **exist** ***within*** the **cell**. They *generally interfere with* the availability of ***normal*** **purine** or **pyrimidine nucleotide**, and ***inhibit*** **synthesis** of **DNA** or **RNA**.

Folic Acid Analogues

Methotrexate (MTX)

Indications;

MTX, ***usually*** **used** in **combination** with **other drugs**, in ***acute*** **Lymphocytic Leukemia**, **Burkitt's Lymphoma** in ***children***, **Breast Cancer**, **Bladder Cancer** and **Head & Neck Carcinomas**.

Low-dose **MTX** is ***effective as*** a **single agent** ***against*** certain **Autoimmune Diseases**; **Psoriasis**, **Rheumatoid Arthritis** and **Crohn's Disease**.

MTX ***should be given with*** **Folinic acid** (**Leucovorin**®); **24 hours** ***after*** *each* **weekly dose** or by the use of ***daily*** **Folic acid** (not in the same day; ***off-days***), although this may ***decrease*** the **efficacy** of **Methotrexate** by *about* 10%, ***but*** this ***reduces severity*** of **adverse effects**.

Monitoring; **CBC**, **liver enzyme tests**, **kidney function tests** and **monitoring** ***for*** **signs of infection**.

Side Effects;

- ***Common Side Effects***; **Nausea**, **vomiting**, **diarrhea**, **mucositis** (**mucosal ulceration**), **stomatitis** and **myelosuppression** (**anemia**, **leukopenia** and **thrombocytopenia**)
- ***Dose-related Side Effects***; **hepatotoxicity**, **acute pneumonitis** & **kidney failure**

Pregnancy; **Category X**; **MTX** is an ***abortifacient*** and is ***commonly*** used in ***combination with*** **Misoprostol** in ***Medical*** **Abortions** and **Ectopic Pregnancy**.

Drug Interactions; **NSAIDs**, **penicillins**, **cephalosporins**, **aminoglycosides**, **proton-pump inhibitors** and **valproates** are ***increase*** **plasma concentrations** of **MTX**.

Pemetrexed (Alimta®)	**Pralatrexate** (Folotyn®)

Pemetrexed and **Pralatrexate** are ***antifolate agents***.

They are **antimetabolite** ***similar*** in ***mechanism*** to **MTX**, in **addition** to ***inhibiting*** **DHFR**, it also ***inhibits*** **thymidylate synthase**.

Pemetrexed ***uses***;

- ***Malignant*** **Mesothelioma** and ***non–small*** **Cell Lung Cancer**.
  - **Mesothelioma** [me-zoe-thee-lee-O-muh] is a ***type*** of **cancer** that occurs in the **thin layer** of **tissue** that ***covers*** the ***majority*** of the **internal organs** (**mesothelium**); ***most common*** area affected is the ***lining*** of the **lungs**.
- **Pemetrexed** is also ***recommended*** in **combination** ***with*** **Carboplatin** for the ***first-line*** **treatment** of ***advanced non–small*** **Cell Lung Cancer**.

Pralatrexate ***uses***; **Relapsed** or **Refractory** ***Peripheral*** **T-cell Lymphoma** (**PTCL**).

Folic acid and **Vitamin B_{12}** (**IM**) ***should be given before first*** **dose** and ***during*** **therapy** and ***after*** **therapy** to ***reduce*** **hematologic** and **GI toxicities**.

Dexamethasone ***should be given*** to ***avoid*** **Pemetrexed** ***infusion*** **skin rashes**.

Purine Analogues

6-Mercaptopurine (6-MP) (Purinethol®)#

6-Mercaptopurine (6-MP) or Mercaptopurine was the *first* of the thiopurine *analogs* found to be *effective* in **cancer therapy** with *immunosuppressant activity*.

Azathioprine is an *immunosuppressant*, **exerts** its *cytotoxic effects* after *conversion to* 6-MP via *metabolism*.

Metabolism; 6-MP is *converted* in the **liver** to the 6-methylmercaptopurine *derivative* or to Thiouric acid (an *inactive* **metabolite** this *reaction* is *catalyzed by* **xanthine oxidase**; Allopurinol *increased* **levels** of 6-MP, thereby *leading* to *excessive* **toxicity**).

Pharmacogenomics;

- Thiopurine S-methyl-transferase (TPMT) *enzyme* is *responsible*, in *part*, for the *inactivation* of 6-Mercaptopurine.
- *Certain* **genetic variations** *within* the TPMT *gene* can *lead to* *decreased* or *absent* TPMT *enzyme activity*.
- TPMT **screening** *should be* **performed** prior to *administration* in *all* **patients** *prescribed* Azathioprine or 6-Mercaptopurine.

Uses; **Acute Lymphatic Leukemia, Crohn's Disease** and **Ulcerative Colitis**.

6-MP **dose** *should be* **reduce** by **75%** (ie, give quarter dose) *when* **used** *concurrently with* **Allopurinol**.

Common Side Effects; **Nausea, vomiting, diarrhea, myelosuppression** and **hepatotoxicity**.

Fludarabine (Fludara®)

Uses; - **Fludarabine** *used primarily* in *low-grade non*-**Hodgkin's Lymphoma** & **Chronic Lymphocytic leukemia (CLL)**.

- **Fludarabine** is **used** in *various combinations* with **Cyclophosphamide, Mitoxantrone, Dexamethasone** and **Rituximab** in the *treatment* of *non* - **Hodgkin's Lymphoma**.

Fludarabine is a *potent* **immunosuppressant** and *increase risk* for *opportunistic infections*, including **fungi, herpes**, and *Pneumocystis jiroveci* **pneumonia (PCP)**; **Patients** *should receive* **PCP prophylaxis** with Co-Trimoxazole at least **3** *times* a **week**, and this *should continue* for *few* **weeks** or may be *delayed up to* **1 year** *after* **stopping** Fludarabine *therapy*.

Fludarabine *should be* **avoided** in *combination* with **Pentostatin (Deoxycoformycin)** for the **treatment** of *refractory* **Chronic Lymphocytic leukemia (CLL)**; *high* **incidence** of **fatal pulmonary toxicity**.

Cladribine (Leustatin®) | Nelarabine (Arranon®)

- **Cladribine** is *used* in **Hairy Cell Leukemia, Chronic Lymphocytic Leukemia (CLL)** and *non*-**Hodgkin's Lymphoma**, and it was *approved* in **Europe** in 2017 for *highly active* **Relapsing-Remitting Multiple Sclerosis (RRMS)**.
- **Nelarabine** is *used* in **T-cell acute lymphoblastic leukemia/lymphoma**.

Thioguanine or Tioguanine (Lanvis®)

- **Thioguanine**, 6-Thioguanine or **Tioguanine** is **used** to *treat* **Acute Myeloid Leukemia (AML)** and **Acute Lymphocytic Leukemia (ALL)**; *not recommended* for *maintenance* **therapy** due to the *high* **risk** of **liver toxicity** *associated with* **vascular endothelial damage**.

Pentostatin or Deoxycoformycin (Nipent®)

- **Pentostatin** or **Deoxycoformycin** is **used** as *single-agent* for *alpha-interferon-refractory* **Hairy Cell Leukemia** and *may* also be **used** in *certain non*-**Hodgkin's Lymphoma**.

Pyrimidine Analogues

5-Fluorouracil (Adrucil®)#

Administration;
Parenterally; IV only (not used orally due to severe GI toxicity).
Topically; skin cancer.
Pharmacogenomics;
- Dihydro-pyrimidine Dehydrogenase (DPD) enzyme is responsible for the detoxifying metabolism of Fluoropyrimidines drugs that includes 5-fluorouracil, Capecitabine and Tegafur (prodrug of 5-Fluorouracil).
- Genetic variations within the DPD gene can lead to reduced or absent DPD activity, DPD deficiency have a significantly increased risk of severe or even fatal drug toxicities.

Uses; - 5-FU is used primarily in Solid Tumors (for example; Colorectal, Breast, Ovarian, Pancreatic and Gastric Carcinomas).
- 5-FU remains the most widely used agent in Colorectal Cancer.

Common Side Effects; Diarrhea, alopecia, severe mucositis, myelosuppression, hand-foot syndrome (Chemotherapy-induced acral erythema) and coronary vasospasm.

Capecitabine (Xeloda®)#

Capecitabine is an oral fluoropyrimidine carbamate with 70–80% oral bioavailability, which is enzymatically converted to 5-Fluorouracil inside the tumor.
Capecitabine is used in the treatment of colorectal and metastatic breast cancer.
Common Side Effects; Diarrhea and hand-foot syndrome.
Warning; Capecitabine may increase the anticoagulant effects of Warfarin increasing the INR several days up to several months after initiating Capecitabine or within one month after stopping the therapy.

Floxuridine (FUDR®)

Floxuridine or 5-Fluorodeoxyuridine is a prodrug, which is converted to 5-FU, it is used in the treatment of GI Adenocarcinoma with Metastasis to Liver, Gallbladder, Bile Ducts.
Floxuridine is given by rapid intra-arterial injection ONLY by or under the supervision of a qualified physician who is experienced in cancer chemotherapy and intra-arterial drug therapy.

Cytidine Analogues

Cytarabine (Ara-C®)#

Cytarabine is given IV, IM, SC and intrathecal (It is not effective when given orally; because of its deamination to the non-cytotoxic uracil arabinoside; ara-U by cytidine deaminase in the intestinal mucosa and liver).
Uses; Acute Myeloid (non-lymphocytic) Leukemia (AML), Acute Lymphocytic Leukemia (ALL), and Meningeal Leukemia (intrathecal; IT administration).
Common Side Effects; Nausea, vomiting, mucositis, myelosuppression and neurotoxicity.
Cytarabine Syndrome; Conjunctivitis, fever, myalgia, bone pain, rash and malaise.
Cerebellar Toxicity when given in high doses, which may lead to ataxia.

Gemcitabine (Gemzar®)#

Gemcitabine is ***indicated*** as;
- **Pancreatic Cancer** [first-line treatment for patients with locally ***advanced*** (nonresectable Stage II or Stage III) or metastatic (Stage IV)].
- **Breast Cancer** (*in* ***combination*** *with* **Paclitaxel**).
- **Ovarian Cancer** (*in* ***combination*** *with* **Carboplatin**).
- ***Non-small*** **Cell Lung Cancer** (*in* ***combination*** *with* **Cisplatin**).
- **Bladder Cancer** (*in* ***combination*** *with* **Cisplatin**); *Off-label.*
- **Cholangiocarcinoma** and ***other*** **Biliary Tract Cancers**; *Off-label.*

Common Side Effects; **Nausea** and **vomiting**, **flu-like syndrome**, **myelosuppression** and **alopecia**.

- ***Rare Side Effects***; **Renal microangiopathy syndromes** (*including* **hemolytic-uremic syndrome**), **hepatic** and **pulmonary** ***toxicity***.

Azacitidine (Vidaza®) | **Decitabine** (Dacogen®)

Uses; **Myelodysplastic Syndromes** (**MDS**) and **Acute Myeloid Leukemia** (**AML**).

II) Alkylating Agents

- **Alkylating agents** ***exert*** their **cytotoxic effects** by **covalently** ***binding*** to **nucleophilic groups** on ***various cell*** **constituents**.
- **Alkylation** of **DNA** ***within*** the **nucleus** probably represent the **major interactions** that lead to **cell death**. However, these drugs react chemically with sulfhydryl, amino, hydroxyl, carboxyl, and phosphate groups of other cellular nucleophiles as well.
- **Alkylating agents** are used in ***combination*** with **other agents** to treat a **wide variety** of **lymphatic** and **solid cancers**.

Nitrogen Mustard

- Nitrogen mustards are cytotoxic chemotherapy agents that are a derivative of mustard gas.

Mechlorethamine or **Chlormethine** or **Mustine** or **HN2** (Mustargen®)

Mechlorethamine is the ***prototype*** of **Alkylating Agents**.
- It can also be **used** in **chemical warfare** where it has the ***code-name*** **HN2**.

Uses; **Hodgkin's Disease**, **Lymphosarcoma**, **Chronic Myelocytic Leukemia**, **Polycythemia Vera** and **Bronchogenic Carcinoma**.

Common Side Effects; ***Severe*** **nausea/vomiting** (90%), **myelosuppression** and **alopecia**.

Cyclophosphamide (Cytoxan®)# (Endoxan®)# (Neosar®)# | **Ifosfamide** (Ifex®)#

Cyclophosphamide is the ***most*** **widely** **used** **Alkylating Agent** with ***broad*** **spectrum**, being **used** either **singly** or as ***part of*** a **regimen** in the **treatment** of a ***wide variety*** of **neoplastic diseases**.

Ifosfamide is an ***analog*** of **Cyclophosphamide**.

- ***Administration***;
  - # **Cyclophosphamide**; **Oral** or **IV**.
  - # **Ifosfamide**; **IV** ***only*** (**Mesna** ***should be*** administered ***concomitantly*** to **avoid internal bleeding**; ***particular*** **hemorrhagic cystitis**).

Uses;

- **Cyclophosphamide** is **used** in ***combination*** *with* ***other*** **antineoplastic agents** to **treat** a ***wide variety*** of **Lymphatic** and **Solid Cancers**; such as **Lymphoma, Multiple Myeloma, Leukemia, Ovarian Cancer, Breast Cancer, Small Cell Lung Cancer, Neuroblastoma** and **Sarcoma**.
- **Cyclophosphamide** is an ***immunosuppressant*** and used for **autoimmune diseases**.
- **Ifosfamide** is **used** in ***combination*** is **used** in ***combination*** *with* ***other*** **antineoplastic agents** to **treat Germ Cell Testicular Cancer**.
- **Ifosfamide** is ***also*** **used** in **Bone Sarcomas** and **Soft Tissue Sarcomas**.

Side Effects;

Hemorrhagic Cystitis, *which can lead to* **Bladder Fibrosis**; **Bladder toxicity** due to **Acrolein** ***other*** **Toxic Metabolites** in the **urine**;

- **Bladder toxicity** can be ***reduced by***;
  - ***Slow*** **IV infusion**.
  - ***Adequate*** **hydration**.
  - **Mesna** ***should be*** **administered** ***concomitantly*** with **Ifosfamide**.

- **Nausea** and **vomiting, myelosuppression** and **alopecia**.
- ***High dose*** of **Ifosfamide** can cause **Neurotoxicity** and **CNS Toxicity** due to **chloroacetaldehyde** ***metabolite***.

Chlorambucil (Leukeran®)#

Chlorambucil is **used** to ***treat*** **Chronic Lymphocytic Leukemia (CLL), Hodgkin Lymphoma** and **non-Hodgkin Lymphoma**.

Chlorambucil is given **orally** **1 hour** ***before*** or **2 hours** ***after*** **meals** (***empty*** **stomach**).

Chlorambucil has been ***largely replaced*** by **Fludarabine** (**Fludara®**) ***especially*** for **Chronic Lymphocytic Leukemia (CLL)**.

Melphalan (Alkeran®)#

- **Melphalan** is ***available*** **orally** and **parenterally**.

It is ***used*** to **treat** **Multiple Myeloma** (**MM**) [plasma cell cancer].

- ***Other uses***;
  - **Melphalan** (**Evomela®**); ***high-dose*** of **conditioning treatment** ***prior*** to **Hematopoietic Progenitor (Stem) Cell Transplantation** in **Multiple Myeloma (MM)**.
  - **Ovarian Cancer, Retinoblastoma, Ocular (uveal) Melanoma** and **Neuroblastoma**.

Bendamustine (Treanda®)

Bendamustine is ***used*** to treat **Chronic Lymphocytic Leukemia (CLL), Multiple Myeloma** and **non-Hodgkin's Lymphoma**. It is ***given*** **IV**.

Thiotepa (Thioplex®)

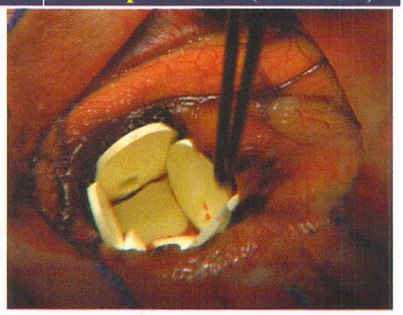
Thiotepa is used in **Adenocarcinoma** of the **Breast** & **Ovary**, and as ***intravesical*** in **Bladder Cancer**.

Nitrosoureas

Nitrosoureas are ***highly*** **lipid-soluble** and are able to ***cross*** the **blood-brain barrier**, making them effective in the ***treatment*** of **brain tumors**.

- **These drugs *appear*** to be ***non-cross-resistant*** with ***other*** **alkylating agents**.

Carmustine (BiCNU®)# | **Lomustine** (CeeNu®)# | **Streptozocin** (Zanosar®)



Carmustine is **used** to ***treat*** *certain types* of **Brain Tumors**, **Hodgkin's Disease**, **non-Hodgkin's Lymphomas** and **Multiple Myeloma**; It is ***given*** **IV** and also ***available as*** an **implantable brain wafer** (**Gliadel®**); **wafer** as an ***adjunct*** to **surgery** & **radiation**.

Carmustine is *also* **used** as **part** of **conditioning regimen** in **Hematological Stem Cell Transplantation**.

Lomustine are **used** in **Brain Tumors** and **Hodgkin's Disease**; It is ***given*** **orally** **ONLY ONCE EVERY 6 WEEKS** [***both*** **physician** and **pharmacist** ***should*** **emphasize** to **patient** that ***only*** **one dose** of the drug is *taken* ***every*** **6 weeks**; ***Severe*** **Myelosuppression**] on ***empty*** **stomach** (no food or drink for 2 hours after to decrease incidence of nausea).

Streptozocin is **used** to ***treat*** **islet cell cancer** *of the* **pancreas**; It is ***given*** **IV**.

Alkyl Sulfonates

Busulfan (Myleran®)# (Bulsulfex®)

Busulfan [bue-SUL-fan] is **used** in ***combination with*** **Cyclophosphamide** as a ***conditioning*** **regimen** prior to **Allogeneic Hematopoietic Progenitor Cell Transplantation**, *especially in* **Chronic Myelogenous Leukemia** (**CML**). It is ***available*** **orally** (**Myleran®**) and **IV** (**Bulsulfex®**).

Toxicity; **Myelosuppression**, **Interstitial Pulmonary Fibrosis** (**Busulfan Lung**), **Seizures**, **Hepatic Veno-Occlusive Disease** (**HVOD**), **Hyperpigmentation** and **Wasting Syndrome**.

Antiepileptic agent is used as ***prophylaxis*** against **Busulfan-induced Seizures**.

Non-Classical Alkylating Agents

Procarbazine (Matulane®)

- **Procarbazine** is an **orally** ***active*** ***Methyl-Hydrazine Derivative***.

Uses;

- **Hodgkin's Lymphoma**; in **MOPP** or **BEACOPP*** ***regimens***.
  - * **MOPP**; **Mechlorethamine**, **Vincristine** (**Oncovin®**), **Procarbazine**, **Prednisolone**.
  - * **BEACOPP**; **Bleomycin**, **Etoposide**, **Doxorubicin** (**Adriamycin®**), **Cyclophosphamide**, **Vincristine** (**Oncovin®**), **Procarbazine**, **Prednisone**.
- **Brain Tumors**; in ***combination with*** **Lomustine** [**CCNU**] & **Vincristine**; **PCV** ***regimen***.
- **Non-Hodgkin's Lymphoma**; in **CEPP*** ***regimens***.
  - * **CEPP**; **Cyclophosphamide**, **Etoposide**, **Procarbazine** and **Prednisone** (***with*** or ***without*** **Bleomycin**).

- It ***weakly*** **inhibits MAO**, so it *can cause* **hypertensive crises** *if associated with* the ingestion of **tyramine-rich foods** such as **aged cheeses**.

Dacarbazine (Dtic-Dome®)

- **Dacarbazine** is **used** to as a ***single agent*** in **metastatic malignant melanoma**.
- It is **used** in ***combination*** in **Hodgkin's disease** and **soft tissue sarcomas**.
- **Dacarbazine** is ***considered to*** be ***highly*** **emetogenic** (**antiemetic agents** are used as **pre-medicated**).

Temozolomide (Temodal®)#

- **Temozolomide** is **used** to as ***first-line*** treatment for **glioblastoma multiforme** (**GBM**) and a ***second-line*** (after **Nitrosourea** and **Procarbazine**) treatment for **anaplastic astrocytoma** (*types of brain tumors*).

Altretamine (Hexalen®)

- **Altretamine** is **used** in ***persistent*** or ***recurrent*** **Ovarian Cancer** ***after*** ***first-line*** **treatment** with a **Cisplatin** and/or **alkylating agent-*based*** **combination**.

Platinum Analogues

Cisplatin (Platinol®)#

Cisplatin is **used** in **Solid Tumors** (**testicular cancer**, **ovarian cancer**, **bladder cancer**, breast cancer head and neck cancer, cervical cancer, lung cancer, mesothelioma, esophageal cancer and brain tumors).

- ***Administration***; **IV infusion**, **Intra-peritoneally** (**IP**) and **Intra-arterially** (**IA**).

Toxicity;

- ***Severe***, ***persistent*** **vomiting** (at least 1 hour after administration and may continue for as long as 5 days).
- **Nephrotoxicity**; ***Dose-related*** and ***cumulative***.
- **Ototoxicity**; **Tinnitus** and/or **hearing *loss***.
- **Neurotoxicity**; **Peripheral neuropathy** and **optic neuritis**.
- **Myelosuppression** and **Hypersensitivity Reactions**.

Carboplatin (Paraplatin®)#

Uses; ***Like*** **Cisplatin**; **Carboplatin** has ***broad-spectrum*** **activity** ***against*** a ***wide range*** of **Solid Tumors**. *However*, in ***contrast*** to **Cisplatin**, it exhibits ***significantly less*** **Nephrotoxicity** and **GI toxicity** and **used** when **patients** ***cannot*** be **vigorously hydrated**, as is *required for* **Cisplatin therapy**.

Side effects and Toxicity;

- ***Mild*** **Nausea** and **Vomiting**.
- **Neurotoxicity**, **Myelosuppression**, **Hepatotoxicity** and **Hypersensitivity**.
- ***Rarely*** **Nephrotoxicity** and **Ototoxicity**.

Oxaliplatin (Eloxatin®)#

Oxaliplatin is **used** for ***treatment*** of **Colorectal Cancer**, ***typically*** in ***combination with*** **Fluorouracil** and **Folinic acid** (**Leucovorin**); **FOLFOX**;

* **FOL**inic acid, **5-F**luorouracil and **OX**aliplatin (**FOLFOX**).

- ***Administration***; **IV infusion**.

Side effects and Toxicity;

- **Neurotoxicity**; **Peripheral neuropathy**.
- **Nausea**, **Vomiting** and **Myelosuppression**.

N.B.; **Nephrotoxicity** and **Ototoxicity** ***less than*** **Cisplatin** and **Carboplatin**.

III) Cytotoxic Antibiotics

- The **Cytotoxic antibiotics** owe their ***cytotoxic action*** primarily to their **interactions** *with* **DNA**, leading to ***disruption*** of **DNA function**.
- **Cytotoxic antibiotics** ***inhibit*** **topoisomerases** (**I** and **II**) and ***produce*** **free radicals** also ***play*** a **major role** in their **cytotoxic effect**.

Anthracyclines

Anthracyclines are used to ***treat*** **various cancers** and ***most important*** and ***widely*** used **anticancer drugs** (**Doxorubicin**; **one** of the ***most important*** **anticancer drugs**).

The ***main side effects*** of **Anthracyclines** is ***irreversible***, **dose-dependent** **CARDIOTOXICITY** (due to **free radical** ***formation and other mechanisms***); ***more common*** with **Daunorubicin** and **Doxorubicin** ***than*** with **Idarubicin** and **Epirubicin**.

Dexrazoxane (**Zinecard**®) is a ***cardio-protective agent*** (chelates iron and thus reduces the number of metal ions complexed with anthracycline and, consequently, decrease the formation of superoxide radicals) has been used to ***protect*** the **heart** ***against*** the **cardiotoxic** of **Anthracyclines**.

All **Anthracyclines** must be ***administered*** **IV** (*due to* ***inactivated*** in the **GI tract**).

* **Extravasation** can ***lead to*** **tissue necrosis**.
* ***Because*** of the ***dark*** **red color**; the **veins** may ***become*** **visible** ***surrounding*** the ***site*** of **infusion**, and **red** ***discoloration*** of **urine** ***may*** **occur**.
* **Dexrazoxane** (**Totect**®) (**Savene**®) is also *available* as **extravasation antidote** for ***treatment*** of **extravasation** *resulting from* **IV Anthracyclines**.

Daunorubicin (Cerubidine®)#

Daunorubicin or **Daunomycin** is the ***first*** **Anthracycline** ***discovered***.

It is **used** to ***treat*** **acute leukemias**.

- In ***contrast to*** **Doxorubicin**, its ***efficacy*** of **Daunorubicin** in **solid tumors** is ***limited***.

Doxorubicin (Adriamycin®) (Adriblastina®)#

Doxorubicin or **Adriamycin** is **one** of the ***most important*** **anticancer drugs** in ***clinical practice***, it also ***called*** 😈 **Red Devil Chemo** 😈 *partly due to* its **red color**.

It has a ***broad*** **spectrum** of ***activity*** and **one** of the ***most effective*** **anticancer drugs** *for* **Solid Tumors**.

It is **used** to ***treat*** **Solid Tumors**; **Cancers** of **Breast**, **Bladder**, **Stomach**, **Lung**, **Ovaries**, **Thyroid**, **Soft Tissue Sarcoma**, **Multiple Myeloma**, **Liver** and ***Others***.

It is **used** to ***treat*** **Leukemias**, **Hodgkin's Lymphoma** and **non-Hodgkin's Lymphoma**.

Doxorubicin Liposomal (**Doxil**®); is a **polyethylene glycol** ***coated*** **liposome-*encapsulated*** *form* of **Doxorubicin** **used** to treat **AIDS-related Kaposi's Sarcoma**, **Ovarian Cancer**, **Multiple myeloma** and *off label for* **Breast Cancers** ***other*** **Solid Tumors**; **Doxorubicin Liposomal** is ***less*** **cardiotoxic** *than* the ***usual*** **formulation**.

Commonly used **Doxorubicin-Containing Regimens**;

Regimen	Agents	Uses
AC	Adriamycin (Doxorubicin) + Cyclophosphamide	Breast cancer
TAC	Taxotere + Adriamycin + Cyclophosphamide	Breast cancer
FAC	5-Fluorouracil + Adriamycin + Cyclophosphamide	Breast cancer
ABVD	Adriamycin + Bleomycin + Vinblastine + Dacarbazine	Hodgkin's lymphoma
BEACOPP	Bleomycin + Etoposide + Adriamycin + Cyclophosphamide + Oncovin (Vincristine) + Procarbazine + Prednisone	Hodgkin's lymphoma
CHOP	Cyclophosphamide + Hydroxydaunorubicin + Oncovin + Prednisone	non-Hodgkin's lymphoma

Idarubicin (Idamycin®)#

Idarubicin is a **4-demethoxy** ***semisynthetic analog*** of **Daunorubicin**, and this ***increases*** its **lipophilicity**.

It is **used** in ***combination with*** **Cytarabine** as a ***first line*** treatment of **Acute Myeloid Leukemia**.

Epirubicin (Ellence®)#

Epirubicin has ***faster*** **elimination** ***lower*** **cardiotoxicity** *than* **Doxorubicin**.

Epirubicin is ***approved*** *as* **adjuvant therapy** in **patients** ***with*** **axillary node tumor** *after* **surgery** ***remove*** of ***primary*** **breast cancer** (**node-positive patients**).

- It is ***also*** **used** in **Breast** and **Ovarian Cancer**, **Gastric Cancer**, **Lung Cancer** and **Lymphomas**.

Valrubicin (Valstar®)

- **Valrubicin** is **used** ***specifically*** in the **treatment** of **Bladder Cancer** (by infusion directly into the bladder; intravesical).

Mitoxantrone (Novantrone®)#

- **Mitoxantrone** or **Dihydroxyanthracenedione** is an ***anthracene compound*** whose ***structure resembles*** the **Anthracycline** ***ring***.
- It is **used** to ***treat***;
  - ***Advanced***, ***hormone-refractory*** **Prostate Cancer** (***combination*** with **Prednisone**).
  - *Low-grade* **non-Hodgkin's Lymphoma**.
  - **Breast Cancer** and **Acute Myeloid Leukemias**.
- **Mitoxantrone** is also **used** to ***treat*** **Multiple Sclerosis** (**MS**).

Others

Bleomycin (Blenoxane®)#

It is **used** in **Squamous Cell Carcinoma**, **Hodgkin's disease**, **non-Hodgkin's lymphoma**, **Testicular Carcinoma** and **Pleural Sclerosing**.

Metabolism; **Bleomycin** is ***inactivated*** by **hydrolase enzyme**;

  * The **enzyme** is ***widely*** **distributed** in **normal tissues** with the ***exception*** of the **skin** and **lungs**, both ***targets*** of **Bleomycin toxicity**.

Bleomycin toxicity;

  # **Skin toxicity**; **Hypertrophic skin changes** and **hyperpigmentation** of the **hands**.

  # **Pulmonary toxicity**; **Pneumonitis** with **cough**, **dyspnea** and **pulmonary fibrosis**.

The **pulmonary fibrosis** that is caused by **Bleomycin** is referred as; **Bleomycin lung**.

Mitomycin (Mutamycin®)#

- **Mitomycin** or **Mitomycin C** is an **antibiotic** *isolated from* ***Streptomyces caespitosus***.

It is **used** in the *treatment of* ***Cancer*** of the **Stomach** or **Pancreas**.

It is *also* **used** in *treatment* of ***Cancer*** of **Anal**, **Bladder**, **Breast**, **Cervical**, **Colorectal**, **Head** and **Neck**, and **non-Small Cell Lung Cancer**.

Common Side effects; - **Hemolytic Uremic Syndrome (HUS)**; ***progressive*** **renal failure**; **hemolytic anemia**, ***low*** **platelet count** and ***permanent*** **kidney failure**.

- **Myelosuppression**, **Nausea/vomiting** and **Fever**.

Dactinomycin or Actinomycin D (Cosmegen®)

- **Actinomycin D** was the ***first antibiotic*** *shown to* have **anti-cancer activity**.
- It is **used** in **Wilms' Tumor** (cancer of the kidneys that typically occurs in children), **Ewing's Sarcoma**, (Ewing's [YOO-ing] sarcoma is a rare type of cancer that occurs in bones) **Gestational Trophoblastic Neoplasm**, **Metastatic Testicular Tumors**, **Childhood Rhabdomyosarcoma**, **Trophoblastic Neoplasm** and *certain types* of **Ovarian Cancer**.
- It is ***also*** **used** as a **radio-sensitizer** (***increase*** the **radio-sensitivity** of **tumor cells**).
- ***Common Side effects***; **Nausea/vomiting**, **mucositis**, **myelosuppression** and **alopecia**.

IV) Microtubule Inhibitors

- **Mitotic spindle**; is an intracellular skeleton (cytoskeleton) that is essential for the movements of structures occurring in the cytoplasm of all eukaryotic cells.
- The **mitotic spindle** ***consists of*** **chromatin** and **microtubules** composed of the protein tubulin.
- The **mitotic spindle** is ***essential for*** **eukaryotic cell division**.

Vinca Alkaloids

- **Vinca alkaloids** are a set of ***anti-mitotic*** and ***anti-microtubule*** ***alkaloid agents*** originally derived from the periwinkle plant *Vinca rosea* and other vinca plants.

Administration and **FDA WARNING**; ***Vinca*** **alkaloids Vincristine - Vinblastine – Vinorelbine**;

* **IV ONLY**; **FATAL** ***if given*** **intrathecally**.

* **Extravasation** *may occurs*.

The ***main side effects*** of **Vinca alkaloids** is;

NEUROTOXICITY (**peripheral neuropathy**, autonomic nervous system dysfunction with orthostatic hypotension, **urinary retention**, and **paralytic ileus** or **constipation**, cranial nerve palsies, ataxia, seizures and coma); **Vincristine** > **Vinblastine** > **Vinorelbine**.

Syndrome of Inappropriate Secretion of Antidiuretic Hormone (**SIADH**); too much antidiuretic hormone and **hyponatremia** impaired water excretion.

Myelosuppression (**Vinblastine**>**Vincristine**) **Nausea/vomiting** and **Alopecia**.

Vincristine (VX) (Oncovin®)#

Vincristine (**VX**) or **Oncovin** is **used** in the *treatment of*;

- **Acute Leukemia**.
- **non- Hodgkin's Lymphoma**.
- **Rhabdomyosarcoma**.
- **Ewing's Sarcoma**.
- **Hodgkin's Lymphoma**.
- **Neuroblastoma**.
- **Wilms' Tumor**.
- **Multiple Myeloma**.

Main Side effects; **Peripheral neuropathy**, **hyponatremia**, **constipation** and **alopecia**.

Liposomal-Vincristine (**Marqibo®**); ***enhances*** **efficacy** and ***decreasing*** the **neurotoxicity**; **FDA approved** in **2012**.

- **Nano-particle-Vincristine** was ***under development*** as of **2014**.

Vinblastine (VBL) (Velban®)#

It is **used** in *treatment of* **Hodgkin lymphoma**, **non-Hodgkin's lymphoma**, **testicular**, **Kaposi's sarcoma**, **breast** and **lung cancer**.

Vinorelbine (VRB) (Navelbine®)#

Vinorelbine (**VRB**) is ***less*** **neurotoxic** than **Vinblastine** and **Vincristine** (**Vinorelbine** < **Vinblastine** < **Vincristine**).

Vinorelbine is **used** as ***first-line*** in *treatment of* ***advanced*** or ***metastatic*** **non-Small Cell Lung Cancer** (**NSCLC**) as a ***single agent*** or in ***combination*** with **Cisplatin**.

- It is **off-label use** in **Breast** and **Ovarian Cancer**.

Vinorelbine ***like*** *other* ***Vinca*** **administered parenterally**;

* **IV ONLY**; **FATAL** *if* ***given*** **intrathecally**.

- **Vinorelbine** is also ***available*** in **oral** ***formulation***; but is ***not approved*** in the **United States**.

Taxanes

- **Taxanes** is a ***plant alkaloids*** *derived from* Pacific yew (*Taxus brevifolia*) and European yew (*Taxus baccata*).

Toxicity; **hypersensitivity reactions** and **neurotoxicity** (**peripheral neuropathy**).

Paclitaxel (Taxol®)#

- **Paclitaxel** was the ***first member*** of the **taxane family**.

Paclitaxel has ***significant activity*** in a **broad range** of **solid tumors**; **ovarian**, *advanced (metastatic)* **breast**, **lung**, **head** and **neck**, **esophageal**, **prostate**, and **bladder cancers** and **AIDS-*related* Kaposi's sarcoma**.

Premedication *with* **Dexamethasone**, **Diphenhydramine** and an **H_2 blocker** to *decrease* **hypersensitivity reactions** to **Paclitaxel**.

Albumin-bound **Paclitaxel** (**Abraxane®**) ***form*** is also ***available*** and used in **metastatic breast cancer**, **lung cancer** and **pancreatic cancer**.

Abraxane® is ***not associated*** with **hypersensitivity reactions** and **neurotoxicity** ***more readily*** **reversible** than **Paclitaxel**.

Docetaxel (Taxotere®)#

Docetaxel or **Taxotere** is a ***semisynthetic*** **taxane** **used** in ***advanced*** **Breast Cancer**, **Lung Cancer**, **Head & Neck Cancer**, **Gastric Cancer** and **Prostate Cancer**.

Abnormal **liver function** ***increase*** **risk** of **Docetaxel**-*associated* ***mortality***.

- **Docetaxel** ***should not*** be **used** if **neutrophil** ***count*** <1500 cells/mm^3.

Severe **Hypersensitivity Reactions** may also occur.

Cabazitaxel (Jevtana®)

Cabazitaxel was **approved** by **FDA** for the ***treatment*** of ***hormone-refractory*** **Prostate Cancer** in **2010**.

- **Cabazitaxel** ***should not*** be **used** if **neutrophil** ***count*** <1500 cells/mm^3.

Severe **Hypersensitivity Reactions** may also occur.

Other

Ixabepilone (Ixempra®)

- It is **used** in ***aggressive metastatic*** or ***locally advanced*** **Breast Cancer**.
- **Ixabepilone** ***should not*** be **used** if **neutrophil** ***count*** <1500 cells/mm^3.
- ***Severe*** **Hypersensitivity Reactions** may also occur.

Eribulin (Halaven®)

- It is a ***microtubule inhibitor*** used in ***metastatic*** **Breast Cancer & Liposarcoma**.

V) Endocrine Therapy

- A **hormone-sensitive cancer** or **hormone-dependent cancer**; is a ***type of cancer*** that is ***dependent on*** a **hormone** *for* **growth**.
- ***Examples***; **breast cancer**, which is ***dependent*** on **estrogens** *like* **Estradiol**, and **prostate cancer**, which is ***dependent*** on **androgens** *like* **Testosterone**.

Glucocorticoids

- **Glucocorticoids** interfere with the ***concentration***, ***distribution*** and ***function*** of **leukocytes**.
- **Glucocorticoids** ***prominently*** **used** in the ***treatment*** of **blood cancers**.

Prednisone (Hostacortin®)#

- **Prednisone** is a ***potent***, ***synthetic***, ***anti-inflammatory*** **corticosteroid** with ***less*** **mineralocorticoid** ***activity*** than **Cortisol**.
- **Prednisone** is ***inactive*** and ***extensively*** **metabolized** in **liver** *via* ***hydroxylation*** to **Prednisolone** (***active*** **metabolite**) and ***excreted*** **renally**.

Prednisone is ***primarily*** employed to ***induce*** **remission** in *patients with* **Acute Lymphocytic Leukemia** and ***both*** **Hodgkin** and **non-Hodgkin Lymphomas**, **Multiple Myeloma** and ***other*** **Blood Cancers**.

Prednisone can be ***found*** in ***several*** **combination chemotherapy regimens**, *like*;

* **BEACOPP**; **Bleomycin** + **Etoposide** + **Adriamycin** + **Cyclophosphamide** + **Oncovin** (**Vincristine**) + **Procarbazine** + **Prednisone** *for* **Hodgkin's Lymphoma**.
* **CHOP**; **Cyclophosphamide** + **Hydroxydaunorubicin** + **Oncovin** + **Prednisone** *for* **non-Hodgkin's Lymphoma**.

Prednisone also ***helps*** to ***decrease*** **nausea** as well as ***promote*** an **appetite**.

Estrogens

- **Estrogens**, *such as* **Ethinyl Estradiol**, had been used in the ***treatment of*** **prostatic cancer**. *However*, they have been ***largely replaced*** by the **GnRH analogs**.

Antiestrogens

Selective Estrogen Receptor Modulators (SERMs)

Tamoxifen (Nolvadex®)#

Tamoxifen is used for ***first-line therapy*** in the *treatment of* both ***early*** and ***advanced*** **estrogen receptor–positive breast cancer**; ***orally***.

- **Tamoxifen** is *also* **used**;
  - ***Prevent*** **estrogen-related gynecomastia**.
  - **Ductal Carcinoma** *in* **Situ** (**DCIS**); abnormal cells in of milk ducts in the breast.
- ***Off-label***; **Ovulation** ***induction***.

Tamoxifen has the ***potential*** to cause **endometrial cancer**.

Side effects; **hot flashes**, **nausea**, **vomiting**, **skin rash**, **vaginal bleeding** and **discharge** (*due to* estrogenic activity), **joint pain** and **thromboembolism**.

Fulvestrant (Faslodex®)#

Fulvestrant is a selective **Estrogen Receptor Degrader** (**SERD**), it **works** by ***binding*** to the **estrogen receptor** and ***destabilizing*** **it**, and ***downregulates*** **estrogen receptors** and ***inhibits*** **breast tumor** ***growth***.

Fulvestrant is ***given*** **IM** for **Hormone Receptor–Positive** ***advanced*** **Breast Cancer**.

- ***Side effects***; ***like*** **Tamoxifen**.

Raloxifene (Evista®)#

Raloxifene is a Selective Estrogen Receptor Modulator (SERM); *estrogenic* in bone, but *anti-estrogenic* in breast and uterus.
Raloxifene is *given orally* for;
- Osteoporosis in *postmenopausal* women.
- *Reduce* the risk of Breast Cancer in *postmenopausal* women *with* osteoporosis.
- *Reduce* the risk of Breast Cancer in women with *high risk* for breast cancer.

- *Side effects*; *like* Tamoxifen.
FDA Black Box Warning; *risk* of *venous thromboembolism* and death *due to* stroke.

Aromatase Inhibitors (AIs)

Aromatase is the *enzyme* that *synthesizes* Estrogen, which *converts* Androgens into Estrogens by a *process called* Aromatization.

Anastrozole (Arimidex®)#	Letrozole (Femara®)#

- Anastrozole and Letrozole are non-steroidal *reversible competitive inhibitor*.
- They are used *in hormone-dependent* breast cancer.
- They are used *to prevent* estrogen-related gynecomastia.
- Letrozole has been used *for* ovarian stimulation.

Side effects; hot flashes, joint pain & osteoporosis (Bisphosphonates are *prescribed*)

Exemestane (Aromasin®)#

- Exemestane is a steroidal, *irreversible inhibitor* of Aromatase.
- Exemestane is used *in hormone-dependent* breast cancer.

Progestins

Megestrol Acetate (MGA) (Megace®)

- MGA is also *commonly* used as a supportive to *treat* severe loss of appetite (anorexia) and muscle wasting (cachexia) in patients *with* cancer or HIV/AIDS.

GnRH Analogue

- They are a drug used to *suppress* production of the sex hormones (Testosterone and Estrogen), particularly in the *treatment* of breast and prostate cancer.

Leuprorelin or Leuprolide (Lupron®)#

Goserelin (Zoladex®)#	Triptorelin (Trelstar®)#

- They are used to *treat hormone-sensitive* cancers of the breast and prostate.
- Leuprolide is available as - Sustained-release intradermal implant
  - SC depot injection
  - IM depot injection
- Goserelin acetate is a SC implant.
- Triptorelin pamoate is injected IM.

Antiandrogens

Flutamide (Eulexin®)#	Nilutamide (Anandron®)#	Bicalutamide (Casodex®)#

- Flutamide, Nilutamide and Bicalutamide are *synthetic*, *non-steroidal* antiandrogens used in the *treatment of* prostate cancer.

Most common side effects; Gynecomastia and breast tenderness.
- Flutamide and Bicalutamide *rarely* cause hepatotoxicity.
- Nilutamide can *cause* visual problems and interstitial pneumonitis.

VI) Monoclonal Antibodies

Rituximab (Rituxan®)#

- **Rituximab** was the ***first*** **monoclonal antibody** to be approved for **cancer**.
- It is **used** *for* **non-Hodgkin's lymphoma**, **chronic lymphocytic leukemia** and **rheumatoid arthritis**.

Severe side effects; ***Severe*** **infusion** ***reactions*** (**fatal**) and **tumor lysis syndrome**.

Trastuzumab (Herceptin®)#

- It is **used** in **Breast Cancer**, **Gastric Cancer** and ***off-label*** in **Pancreatic Cancer**.

Severe side effects; **heart failure** (*worsened with* **Anthracyclines**) & **allergic reactions**.

Pertuzumab (Perjeta®)#

- **Pertuzumab** used in ***combination*** with **Trastuzumab** and **Docetaxel** for the treatment of ***metastatic*** **HER2-positive breast cancer**.

Severe side effects; **heart failure** (*worsened with* **Anthracyclines**) & **allergic reactions**.

Bevacizumab (Avastin®)#

- **Bevacizumab** used as ***first-line*** in **metastatic colorectal cancer**.
- It is *also* **used** in **lung cancer**, **glioblastoma**, and **renal-cell carcinoma**.
- It is *also* **used** for ***age-related*** **macular degeneration** (injection into the eye).

Severe side effects; **hypertension** and ***heightened*** **risk** of **bleeding**.

Cetuximab (Erbitux®)# | Panitumumab (Vectibix®)#

- **Cetuximab** and **Panitumumab** are an **epidermal growth factor receptor** (***EGFR***) ***inhibitor*** **used** for in ***metastatic*** **colorectal cancer**.
- **Cetuximab** also **used** in ***metastatic*** **non-small cell lung cancer** & **head** & **neck cancer**

Others

Ramucirumab (Cyramza®)	Gastric Cancer, non-small Cell Lung Cancer, Colorectal Cancer
Pembrolizumab (Keytruda®)	Metastatic Melanoma, non-small Cell Lung Cancer, Head & Neck Squamous Cell Carcinoma and classical Hodgkin Lymphoma (cHL)
Olaratumab (Lartruvo®)	Soft-tissue Sarcoma (STS)
Ofatumumab (Arzerra®)	Chronic Lymphocytic Leukemia (CLL)
Obinutuzumab (Gazyva®)	Chronic Lymphocytic Leukemia (CLL) and Follicular Lymphoma
Nivolumab (Opdivo®)	Metastatic Squamous non-small Cell Lung Cancer, Metastatic Melanoma, Renal Cell Cancer, Urothelial Carcinoma and Hepatocellular Carcinoma (HCC)
Necitumumab (Portrazza®)	Metastatic Squamous non-small Cell Lung Cancer
Ipilimumab (Yervoy®)	Metastatic Melanoma
Ibritumomab (Zevalin®)	non-Hodgkin's Lymphoma
Elotuzumab (Empliciti®)	Multiple Melanoma
Durvalumab (Imfinzi®)	Urothelial Carcinoma
Daratumumab (Darzalex®)	Multiple Myeloma
Brentuximab (Adcetris®)	Hodgkin Lymphoma and Anaplastic Large-cell Lymphoma
Blinatumomab (Blincyto®)	Precursor B-cell Acute Lymphoblastic Leukemia
Avelumab (Bavencio®)	Metastatic Merkel Cell Carcinoma
Atezolizumab (Tecentriq®)	Urothelial Carcinoma & Metastatic non-small Cell Lung Cancer
Alemtuzumab (Campath®)	B-cell Chronic Lymphocytic Leukemia

VII) Tyrosine Kinase Inhibitor

- **Tyrosine kinases** are a ***family*** of **enzymes** that are *involved* in ***several*** **important processes** within a cell, including **signal transduction** and **cell division**.

Imatinib (Gleevec®) (Glivec®)#

- **Imatinib mesylate** is a **Tyrosine Kinase Inhibitor**, ***specific*** for ***abnormal*** **BCR-ABL tyrosine kinase** *produced* by **Philadelphia chromosome** in **CML/ALL**.
  - Philadelphia chromosome is a specific genetic abnormality in chromosome 22 of leukemia cancer cells.
- **Imatinib** is ***orally active*** and ***highly*** **bioavailable**, **metabolized** *via* **CYP450** and ***excreted*** in the **feces**.

Imatinib used to **treat Philadelphia chromosome positive (Ph+)**; **Chronic Myelogenous Leukemia (CML)** and **Acute Lymphoblastic Leukemia (ALL)**.

- ***Other Uses***; - **Gastrointestinal Stromal Tumors (GIST)**.
  - **Myelodysplastic/Myeloproliferative Diseases (MDS/MPD)**.
  - **Aggressive Systemic Mastocytosis (ASM)**.
  - **Hypereosinophilic Syndrome (HES)** and/or **Chronic Eosinophilic Leukemia (CEL)**.
  - **Dermatofibrosarcoma Protuberans (DFSP)**.
- ***Common Side Effects***; **Edema**, **skin rash**, **headache**, **fatigue**, **myelosuppression** and **arthralgia**.

Severe Side Effects; **Fluid Retention** and *risk of* **severe CHF**.

Nilotinib (Tasigna®)#

Nilotinib, *structurally related* to **Imatinib**, it was ***approved*** to *treat* **Imatinib-*resistant*** **Ph+ Chronic Myelogenous Leukemia (CML)**.

- **Nilotinib** is also **used** to *treat* ***newly*** **diagnosed Ph+ CML**.
- **Nilotinib** is off-label use in **Ph+ ALL** and **Gastrointestinal Stromal Tumors (GIST)**.
- ***Common Side Effects***; **Skin rash**, **headache**, **fatigue**, **nausea**, **diarrhea** and **arthralgia**.

Severe Side Effects; **Fluid Retention** and **QT prolongation**.

Dasatinib (Sprycel®)#

Dasatinib, *like* **Imatinib**, it is **used *orally*** to treat **Ph+**; **Chronic Myelogenous Leukemia (CML)** and **Acute Lymphoblastic Leukemia (ALL)**.

- ***Common Side Effects***; **Edema**, **skin rash**, **headache**, **fatigue**, **diarrhea** and **myelosuppression**.

Severe Side Effects; **Pulmonary Arterial Hypertension**.

Erlotinib (Tarceva®)#

Erlotinib is **Tyrosine Kinase-Epidermal Growth Factor Receptor (EGFR) Inhibitor**, it is **used *orally*** to treat **non-small Cell Lung Cancer** and **Pancreatic Cancer**.

- ***Common Side Effects***; **Skin rash**, **anorexia**, **fatigue**, **nausea**, **diarrhea** and **arthralgia**.

Severe Side Effects (*rare*); **Pneumonitis** and **Pulmonary fibrosis**.

Lapatinib (Tykerb®)#

- **Lapatinib** is a **Tyrosine Kinase Inhibitor**, **used** to treat ***metastatic* HER2-*positive* Breast Cancer** (in combination with **Capecitabine** or **Letrozole**).
- ***Common Side Effects***; **Rash, diarrhea, fatigue, hand & foot syndrome** and **myelosuppression**.

Sorafenib (Nexavar®)# | Sunitinib (Sutent®)#

- **Sorafenib** and **Sunitinib** are ***oral* Tyrosine Kinase Inhibitor**, used ***mainly*** in **Renal Cell Carcinoma**.
- ***Uses***; - **Sorafenib**; - ***Advanced* Renal Cell Carcinoma**.
  - ***Advanced* Primary Liver Cancer**.
  - ***Radioactive Iodine Resistant Advanced* Thyroid Carcinoma**.
  - **Sunitinib**; - **Renal Cell Carcinoma**.
  - **Imatinib-*resistant* Gastrointestinal Stromal Tumor (GIST)**.
  - **Pancreatic Neuroendocrine Tumors**.
- ***Most Common Side Effects***; **Rash, diarrhea, fatigue, hand & foot skin reaction syndrome, hypertension** and **myelosuppression**.
- ***Other Agents*** are **used** in **Renal Cell Carcinoma (RCC)**;

Pazopanib (Votrient®)	Advanced Renal Cell Carcinoma and Soft Tissue Sarcomas.
Temsirolimus (Torisel®)	Advanced Renal Cell Carcinoma
Everolimus (Afinitor®)	Renal Cell Carcinoma , Breast Cancer and Neuroendocrine Tumors
Interleukin-2 or **Aldesleukin** (Proleukin®)	Metastatic Renal Cell Carcinoma and Metastatic Melanoma
Bevacizumab (Avastin®)	Renal Cell Carcinoma, metastatic Colorectal Cancer, Lung Cancer, Glioblastoma, and Age-related Macular Degeneration.

VIII) Topoisomerase Inhibitors

- ***Inhibition*** of **topoisomerase II *enzyme*** (which aids in **DNA *unwinding***), ***prevents* re-ligation** of the **DNA strands**, and by doing so causes **DNA strands** to ***break*** (Cancer cells rely on this enzyme more than healthy cells, since they divide more rapidly).

Podophyllotoxin Derivatives

Etoposide (Toposar®)# | Teniposide (Vumon®)#

- **Etoposide** and **Teniposide** are ***semisynthetic derivative*** of **Podophyllotoxin** from the ***rhizome*** of the wild mandrake (*Podophyllum peltatum*).
- **Etoposide** is **used** *for* ***refractory* Testicular Cancer** and **Small-Cell Lung Cancer**.
- **Teniposide** is **used** for ***refractory childhood* Acute Lymphoblastic Leukemia**.
- ***Common Side Effects***; **Nausea, vomiting, myelosuppression** and **alopecia**.

Camptothecins

Topotecan (Hycamtin®)# | Irinotecan (Campto®)#

- **Camptothecins** are ***plant alkaloids*** isolated from Chinese tree (*Camptotheca*; Happy tree)
- **Topotecan** is **used** in ***metastatic* Ovarian Cancer, Cervical Cancer** and **Small-Cell Lung Cancer**.
- **Irinotecan** is **used** *with* **5-FU** & **Leucovorin** for ***treatment*** of **Colorectal Carcinoma**.
- ***Common Side Effects***; **Diarrhea, nausea, vomiting, myelosuppression** and **alopecia**.

IX) Non-Classified

Interferon Alfa-2a (Roferon®-A) | Interferon Alfa-2b (Intron® A)

- **Interferon-α-2a** is *approved for*; **hairy cell leukemia, chronic myelogenous leukemia** and **AIDS-related Kaposi sarcoma.**
- **Interferon-α-2b** is *approved for*; **hairy cell leukemia, melanoma, AIDS-related Kaposi sarcoma,** and **follicular lymphoma.**
- ***Common side effects***; **Flu-like symptoms** and **GI upset.**

L-Asparaginase (Kidrolase®)

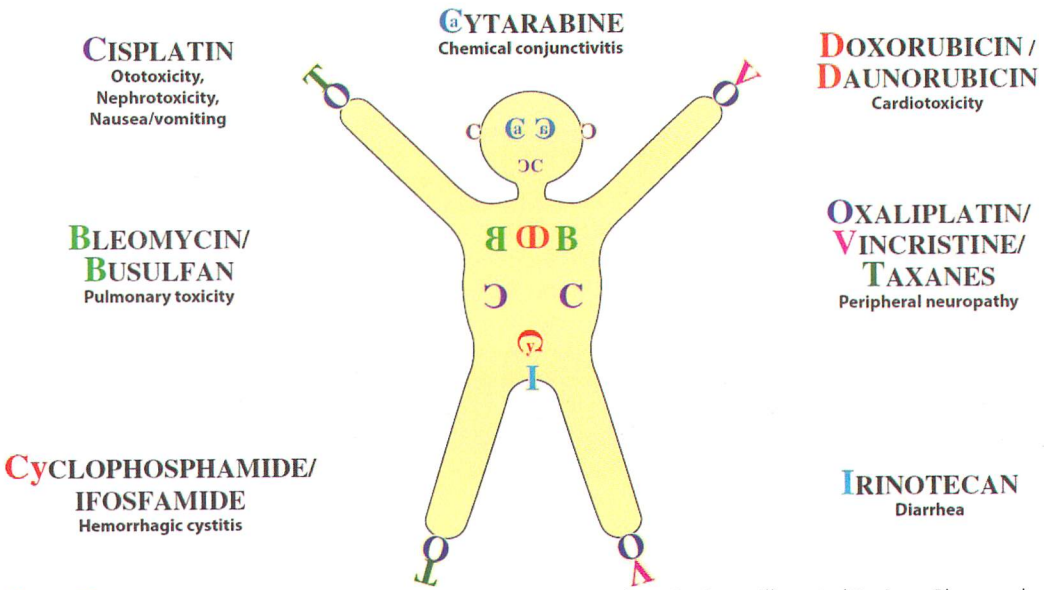
- *Some* **neoplastic cells** *require* an **external source** of **Asparagine** because of ***limited capacity*** to **synthesize *sufficient* amounts** to ***support*** **growth** and **function.**
- **Asparaginase** works by ***breaking down*** **Asparagine.**
- **Pegaspargase** is a **PEGylated *formulation*** of **Asparaginase.**
- **Asparaginase** is **used** to treat ***childhood*** **acute lymphocytic leukemia.**

Abiraterone Acetate (Zytiga®)

- **Abiraterone acetate** is a **steroidal CYP17A1 *inhibitor*** (**Androgen synthesis inhibitor**) which is **used** in ***combination*** with **Prednisone** in **metastatic castration-resistant prostate cancer** (hormone-resistant or hormone-refractory prostate cancer).
- ***Side effects***; **Hypertension, hypokalemia, fluid retention, urinary tract infection** and **hepatotoxicity** *may occur.*

Enzalutamide (Xtandi®)

- **Enzalutamide** is an **oral *synthetic* non-steroidal antiandrogen.**
- **Enzalutamide** is **used** in **metastatic castration-resistant prostate cancer.**
- ***Side effects***; **asthenia, back pain, fluid retention** and **risk of seizure.**



Chemo Man; most common toxicities of Cancer Chemotherapy; Figure from Lippincott Illustrated Reviews: Pharmacology

X) Others and Newly Approved Agents

Ado-Trastuzumab Emtansine (Kadcyla®)

- **Ado-Trastuzumab Emtansine** or **Trastuzumab Emtansine** (**DM1**) is an ***antibody-drug conjugate consisting*** of the ***monoclonal antibody*** **Trastuzumab** ***linked to*** the ***cytotoxic agent*** **Emtansine** (***microtubule inhibitor***).
- It was ***approved*** *specifically* for **treatment** of **HER2-*positive metastatic* breast cancer** in ***patients*** who have been ***treated*** **previously** with **Trastuzumab** and **Taxanes**, ***separately*** or in ***combination***, and who have ***already*** been ***treated for metastatic*** **breast cancer** or ***developed*** **tumor recurrence** ***within*** **6 months** of **adjuvant therapy**.

Inotuzumab Ozogamicin (Besponsa®) | Gemtuzumab Ozogamicin (Mylotarg®)

- **Inotuzumab Ozogamicin** and **Gemtuzumab Ozogamicin** is an ***antibody-drug conjugate consisting*** of the ***monoclonal antibody*** **Inotuzumab** (CD22-directed antibody) or **Gemtuzumab** (CD33-directed antibody) ***linked to cytotoxic agent*** **Ozogamicin** (**Calicheamicins**).
- **Inotuzumab Ozogamicin** was ***approved*** for **treatment** of **adults** with ***relapsed*** or ***refractory*** **B-cell *precursor* Acute Lymphoblastic Leukemia** (**ALL**).
- **Gemtuzumab Ozogamicin** was ***approved*** for ***newly diagnosed*** or ***relapsed*** or ***refractory*** **CD33-*positive* Acute Myeloid Leukemia** (**AML**).
- ***Warning***: **Hepatotoxicity**.

Bortezomib (Velcade®) | Carfilzomib (Kyprolis®) | Ixazomib (Ninlaro®)

- **Bortezomib**, **Carfilzomib** and **Ixazomib** are a ***proteasome inhibitor***, an **enzyme** that ***degrades*** *unwanted* **cellular proteins**. ***Inhibition*** of this enzyme results in a ***build-up*** of **polyubiquinated proteins**, which may cause **cell cycle *arrest***, ***apoptosis***, and ***inhibition*** of **tumor growth**.
- They are **used** for ***relapsed*** or ***refractory*** **Multiple Myeloma**.

Crizotinib (Xalkori®) | Alectinib (Alecensa®) | Ceritinib (Zykadia®)

- **Crizotinib**, **Alectinib** and **Ceritinib** are a **Tyrosine Kinase Inhibitor**; **ALK** (Anaplastic Lymphoma Kinase) & **ROS1** (c-ROS Oncogene 1) ***inhibitor***.
- **Crizotinib** is used for ***metastatic*** **ALK-positive** or **ROS1-*positive*** **non-small Cell Lung Cancer**. **Alectinib** and **Ceritinib** are used for ***metastatic*** **ALK-positive non-small Cell Lung Cancer**.

Omacetaxine (Synribo®)

- **Omacetaxine** is a ***protein synthesis inhibitor*** used to treat **Chronic Myeloid Leukemia** (**CML**).

Ziv-Aflibercept (Zaltrap®)

- **Ziv-Aflibercept** is a ***recombinant*** **fusion protein**, ***inhibits*** **tumor angiogenesis**.
- ***Indication***; in ***combination*** with **5-Fluorouracil**, **Leucovorin**, **Irinotecan** (**FOLFIRI**) for ***metastatic*** **Colorectal Cancer** that is ***resistant*** to or has ***progressed*** after an **Oxaliplatin *regimen***.

Estramustine (Emcyt®)

- **Estramustine** is an **Estrogen/Nitrogen Mustard/Anti-microtubule agent**, was *approved for* **Prostate Cancer**.

Vismodegib (Erivedge®)

- **Vismodegib** is a **Hedgehog (Hh) pathway inhibitor**, this ***pathway*** is **pathogenetically *relevant*** in *more than* **90%** of **Basal-Cell Carcinomas (BCC)**.

Pomalidomide (Pomalyst®)

- **Pomalidomide** is a ***thalidomide analog*** act as ***anti-angiogenic*** (inhibit angiogenesis) and ***immunomodulator***.
- It was ***approved*** for ***relapsed*** and ***refractory*** **Multiple Myeloma**.

Denileukin Diftitox (Ontak®)

- **Denileukin Diftitox** is an ***engineered*** **protein** *combining* **Interleukin-2** and **Diphtheria toxin**, it is **used** for ***persistent*** or ***recurrent*** **Cutaneous T-Cell Lymphoma (CTCL)**.

Bexarotene (Targretin®)

- **Bexarotene** is a ***third-generation*** **retinoid**, used in ***refractory*** **Cutaneous T-cell Lymphoma (CTCL)**.

Romidepsin (Istodax®)

- **Romidepsin** is *obtained* **naturally** from ***Chromobacterium violaceum*** **bacterium** and **works** by ***blocking*** **Histone Deacetylases enzymes**, thus ***inducing*** **apoptosis**.
- It was ***approved*** for ***Cutaneous*** **T-cell lymphoma** and ***Peripheral*** **T-cell lymphoma**.

Vorinostat (Zolinza®)	Belinostat (Farydak®)	Entinostat	Mocetinostat

- **Vorinostat**, **Belinostat**, **Entinostat** and **Mocetinostat** are **Histone Deacetylase (HDAC) Inhibitor**.
- ***Uses***;
  - **Vorinostat**; **Cutaneous T-Cell Lymphoma (CTCL)**.
  - **Belinostat**; ***relapsed*** or ***refractory*** **Peripheral T-cell Lymphoma**.
  - **Entinostat** and **Mocetinostat**; in clinical trials

Tyrosine Kinase Inhibitors	
Dabrafenib (Tafinlar®)	BRAF V600E mutation-positive advanced Melanoma and Non-small Cell Lung Cancer (NSCLC).
Trametinib (Mekinist®)	
Vemurafenib (Zelboraf®)	BRAF V600E mutation-positive advanced melanoma
Cabozantinib (Cabometyx®)	Advanced Renal Cell Carcinoma (RCC) and metastatic Medullary Thyroid Cancer (MTC).
Bosutinib (Bosulif®)	Philadelphia-positive (Ph+) Chronic Myelogenous Leukemia (CML).
Ponatinib (Iclusig®)	Chronic Myeloid Leukemia (CML) and Philadelphia–positive (Ph+) Acute Lymphoblastic Leukemia (ALL).
Axitinib (Inlyta®)	Advanced Renal Cell Carcinoma.
Regorafenib (Stivarga®)	Metastatic Colorectal Cancer, Advanced Gastrointestinal Stromal Tumors and Hepatocellular Carcinoma.
Ruxolitinib (Stivarga®)	Myelofibrosis and Polycythemia Vera
Vandetanib (Caprelsa®)	Metastatic Medullary Thyroid Cancer (MTC).

Immunosuppressants

- **Immunosuppressantsts**; are **drugs** that ***inhibit*** or ***prevent*** **activity** of the **immune system**.
- **Immunosuppressantsts** are **used** in:
  - ***Prevent*** the **rejection** of **transplanted organs** and **tissues**.
  - ***Treat*** **autoimmune diseases** (e.g., **rheumatoid arthritis, multiple sclerosis, myasthenia gravis, psoriasis, vitiligo, systemic lupus erythematosus, sarcoidosis, focal segmental glomerulosclerosis, Behcet's Disease, pemphigus, Crohn's disease** and **ulcerative colitis**).
  - ***Other*** **non-autoimmune inflammatory diseases**; *such as* **ankylosing spondylitis**.
- ***Classification***; **I) Glucocorticoids**; *see hormones*
  II) Calcineurin Inhibitors.
  III) Mechanistic Target Of Rapamycin (mTOR) Inhibitors.
  IV) Mycophenolates.
  V) Immunomodulatory Derivatives of Thalidomide (IMiDs).
  VI) Cytotoxic Agents.
  VII) Antibodies.

Calcineurin (CaN) Inhibitors

- **Calcineurin** (**CaN**) is a **Calcium** and **Calmodulin** ***dependent*** **Serine/Threonine protein Phosphatase**, It ***activates*** the **T cells** of the **immune system**.

Cyclosporine (Sandimmun Neoral®)#

Cyclosporine is a ***calcineurin inhibitor***, is a ***lipophilic*** **cyclic polypeptide** *extracted from* the **soil fungus** *Beauveria nivea*.

Cyclosporine is **used** (orally or IV) for **prevent organ rejection** in **organ transplantation** (**Kidney**, **Liver** and **Heart**), **rheumatoid arthritis, psoriasis, Crohn's disease** and **nephrotic syndrome**.

Cyclosporine eye drops (**Restasis®**) *used for* **KeratoConjunctivitis Sicca** (*severe dry eye syndrome*).

- ***Metabolism***; primarily by **CYP3A4**.

Toxicity; **NEPHROTOXICITY**, **hypertension, hyperglycemia, liver dysfunction, hyperkalemia, altered mental status, seizures** and **hirsutism**.

Tacrolimus (Prograf®)#

Tacrolimus is a **macrolide** ***calcineurin inhibitor*** that is *isolated from* the **soil fungus** *Streptomyces tsukubaensis*.

Tacrolimus is ***preferred over*** **Cyclosporine** *because*; ***increased*** **potency (10–100 times)**, ***decreased*** **episodes of rejection**.

Tacrolimus is **used** (orally or IV) for **prevent organ rejection** in **organ transplantation** (**Kidney**, **Liver** and **Heart**).

Tacrolimus ***ointment*** (**Protopic®**); used for **atopic dermatitis, psoriasis** and **vitiligo**.

- ***Metabolism***; primarily by **CYP3A4**.

Toxicity; **NEPHROTOXICITY**, **NEUROTOXICITY**, **hyperglycemia, hypertension** and **hyperkalemia**.

Pimecrolimus (Elidel®)#

Pimecrolimus like **Tacrolimus**. It is available as a **topical cream**; used for **atopic dermatitis, psoriasis** and **vitiligo**.

Mechanistic Target Of Rapamycin (mTOR) Inhibitors

- **Mechanistic Target Of Rapamycin** (**mTOR**), which is a **Serine/Threonine-*specific*** **protein kinase**. **mTOR *regulates*** **cellular metabolism**, **growth** and **proliferation**.
- **mTOR *inhibitors*** include; **Sirolimus** (**Rapamycin**) as well as its ***analogs*** (called "**rapalogs**") such as **Everolimus** and **Temsirolimus**.

Sirolimus or Rapamycin (Rapamune®)

- **Sirolimus** is a **macrolide** produced by *Streptomyces hygroscopicus* and is ***structurally similar*** to **Tacrolimus**.
- It is **used** in **renal transplantation** and for **LymphAngioleioMyomatosis** (**LAM**).
- ***Metabolism***; primarily by **CYP3A4**.

Sirolimus is **used** in **coronary stent coating**; ***Antiproliferative action***; ***inhibit*** **restenosis** of the **blood vessels** by ***reducing*** **proliferation**.

Side effects; **HYPERLIPIDEMIA**, **headache**, **nausea** and **diarrhea**, **leukopenia** and **thrombocytopenia**.

Temsirolimus (**Torisel®**); an **IV** ***prodrug*** of **Sirolimus**; **used** in **renal cell carcinoma**.

Everolimus (Zortress®) (Certican®) (Evertor®) (Afinitor®) (Votubia®)

It is **used** in; - **Renal transplantation**. - **Advanced kidney cancer** and **breast cancer**.
- **Neuroendocrine tumors** (**NET**) of **GI**, **lung** or **pancreas**.

- **Zortress®**, **Certican®** and **Evertor®** ***brands*** are **used** **transplantation medicine**.
- **Afinitor®** and **Votubia®** ***brands*** are **used** in **oncology**.
- ***Side effects***; like **Sirolimus**.

Mycophenolates

- **Mycophenolic acid** (**Mycophenolate**) ***inhibits*** an **enzyme** needed for the ***growth of*** **T cells** and **B cells**. **Mycophenolic acid** was ***isolated from*** the mold *Penicillium glaucus*.

Mycophenolate Mofetil (CellCept®)# | Mycophenolate Sodium (Myfortic®)#

Mycophenolate Mofetil and **Mycophenolate Sodium** are ***hydrolyzed to*** **Mycophenolic Acid** (*active moiety*).

Mycophenolic Acid is **used** in **solid organ transplant** (**Kidney**, **Liver** & **Heart**) in ***combination with*** **Corticosteroids** and **Cyclosporine** or **Tacrolimus**.

Toxicity; **GI DISTURBANCES** (**nausea** and **vomiting**, **diarrhea**, **abdominal pain**) **headache**, **hypertension** and ***reversible*** **myelosuppression** (*primarily* **neutropenia**).

Pregnancy; **Mycophenolic acid** is *associated with* **miscarriage** and **congenital malformations**.

Mycophenolate Sodium (**Myfortic®**); ***delayed-release*** **enteric-coated** **tablets**; to ***minimize*** the **GI side effects** *associated with* **Mycophenolate Mofetil**.

Immunomodulatory Derivatives of Thalidomide (IMiDs)

Thalidomide was first marketed in 1957 as a **sedative drug** but it was withdrawn from the market in the 1960s because of its **disastrous teratogenic effects** (**Category X**) when used during pregnancy (**malformation of the limbs**; about 10,000 cases were reported of infants and only 40% of these children survived).

Thalidomide (**Immunoprin®**) is an ***immunomodulatory drug*** and the **prototype** of the **Thalidomide class**.

- **Thalidomide** is ***currently used*** in the treatment of **multiple myeloma** and of a ***complication of*** **leprosy**.

Lenalidomide (Revlimid®)

- **Lenalidomide** is a ***derivative of*** **Thalidomide** used in **multiple myeloma** and **myelodysplastic syndromes**.

Pregnancy; Like **Thalidomide**; **Category X**.

Pomalidomide (Pomalyst®)

- **Pomalidomide** is a ***newer*** **oral IMiD** that is **FDA** ***approved*** in **2013** for ***treatment relapsed*** and ***refractory*** **multiple myeloma**.

Cytotoxic Agents

Azathioprine (Imuran®)#

- **Azathioprine** was the ***first agent*** to **achieve** ***widespread*** use in **organ transplantation**.
- **Azathioprine** is a ***prodrug*** of **Mercaptopurine** and, ***like*** **Mercaptopurine**, ***functions*** as an **antimetabolite** (see cancer chemotherapy).
- **Azathioprine** has been ***more widely*** **used** *than* **Mercaptopurine** for **immunosuppression**.

Uses; **Kidney Transplantation** and **Autoimmune Diseases** (such as **rheumatoid arthritis**, **Crohn's disease** and **ulcerative colitis**).

- ***Common Side Effects***; **Nausea**, **vomiting**, **diarrhea**, **myelosuppression** and **hepatotoxicity**.

Cyclophosphamide (Cytoxan®)# (Endoxan®)#

- **Cyclophosphamide** is an ***alkylating agent*** **one** of the ***most*** **efficacious immunosuppressive drugs** ***available*** (see cancer chemotherapy).

Uses; **Cancer**, **Organ Transplantation** and **Autoimmune Diseases**.

Side Effects; - **Hemorrhagic Cystitis**, *which can lead to* **Bladder Fibrosis**.
- **Nausea** and **vomiting**, **myelosuppression** and **alopecia**.

- **Methotrexate**, **Chlorambucil**, **Leflunomide**, **Teriflunomide**, **Hydroxychloroquine** and **Sulfasalazine** are ***other*** **immunomodulatory agents** used in **Autoimmune Diseases**; *like* **Rheumatoid Arthritis** (see Musculoskeletal chapter).

Immunosuppressive Antibodies

Monoclonal Antibodies (mAbs)

Muromonab-CD3 (Orthoclone OKT®3)

Uses; **Corticosteroid-*resistant acute*** **rejection** of **kidney**, **heart**, and **liver allografts**.

- **Muromonab-CD3** has been **voluntary** ***withdrawal*** from the **market** in **2009** *due to* the **availability** of ***newer*** **biologic drugs** with ***similar*** **efficacy** and ***fewer*** **side effects**.

Basiliximab (Simulect®) | Daclizumab (Zenapax®) (Zinbryta®)

- **Basiliximab** is approved in 1998 for used in ***prophylaxis*** of **acute organ rejection** in **renal transplantation** in ***combination with*** **Cyclosporine** and **Corticosteroids**.
- **Daclizumab** was ***approved*** in 1997 by the FDA for use in ***prophylaxis*** of **acute organ rejection** in **renal transplantation**, in 2009 it ***announced*** that it *was* **discontinuing**.
  - In May 2016 the FDA approved **Daclizumab** for the treatment of ***relapsing*** **multiple sclerosis**.
  - In March 2018 **Daclizumab** (**Zinbryta®**) is ***voluntary*** **worldwide market withdrawal** due to ***life-threatening*** events, **liver failure**, and **autoimmune hepatitis**.

Polyclonal Antibodies (pAbs)

Antilymphocyte Globulin (ALG)

Antithymocyte Globulin (ATG) (ATGAM®)

- **Anti-lymphocyte globulin** (**ALG**) and **Anti-thymocyte globulin** (**ATG**) are an ***infusion*** of **animal-antibodies** ***against*** **human T cells** which is **used** in the ***treatment*** of **acute rejection** in **organ transplantation** and **aplastic anemia**. **ALG** is ***less commonly*** **used** than the **ATG**.

Others

Belatacept (Nulojix®)

- **Belatacept** is a ***fusion*** **protein** which acts as a ***selective*** **T-cell costimulation** ***blocker*** by ***binding to*** **CD80** and **CD86** ***receptors*** on **antigen presenting cells** (**APC**).
- ***Uses***; in ***combination*** with **Basiliximab**, **Mycophenolate Mofetil** and **Corticosteroids** to ***prevent*** **kidney transplant rejection** in ***adult*** **Epstein-Barr virus** (**EBV**) **seropositive**.

Immunoglobulin Therapy

- **Immunoglobulin therapy**; is the use of a ***mixture*** of **antibodies** (**immunoglobulins**) to ***treat*** a *number* of **health conditions**. **Human immunoglobulin** is *made from* ***human*** **blood plasma**.
- **Immunoglobulin** ***formulations*** are also ***available*** *including* (***Not*** **Vaccines**).
  - **Immune Globulin Intravenous** (**IGIV**).
  - **Rh$_0$(D) Immune Globulin**.
  - **Hepatitis B Immunoglobulin** (**HBIG**).
  - **Rabies immunoglobulin** (**RIG**).
  - **Tetanus Immune Globulin** (**TIG**).
  - **VZV** (**Varicella Zoster Virus**) **Immune Globulin**.

Immune Globulin Intravenous (IGIV) (Flebogamma®) (Liv-Gamma®)

- This **immunoglobulin preparation** (*usually* **IgG**) is *prepared from* **pools** of **thousands** of **healthy donors**.

\# **IGIV** ***therapy*** is **used** in a **variety of conditions**, ***ranging from*** **immunoglobulin deficiencies** *to* **autoimmune disorders** *to* **HIV disease** *to* **bone marrow transplantation**.

- ***Mechanisms of action***; exact mechanism is still unknown.
- The ***effects*** ***last*** a ***few*** **weeks**.
- ***Common side effects***; **pain** at the ***site of injection***, **muscle pain** and **allergic reactions**.

Rh$_0$(D) Immune Globulin (RhoGAM®) (Rhophylac®)

- **Rh$_0$(D) Immune Globulin** ***contains*** **human IgG antibodies** ***against*** **Rh$_0$(D) antigen** of **red cell**.

\# ***Used*** in **Rh-negative mother** ***within*** **24–72 hours** ***after*** the **birth** of an **Rh-positive infant**, to ***prevent*** **Rh hemolytic disease** of the ***new-born*** in ***subsequent*** **pregnancies**.

- **Rh$_0$(D) Immune Globulin** is ***administered*** (300 mcg) to **mother** & ***must not*** be **given** to **infant**.

Hepatitis B Immunoglobulin (HBIG) (HepaGam B®)

- **HBIG** ***approved*** for **HBV** ***recurrence*** ***following*** **liver transplantation** and ***provide*** **post-exposure** ***prophylaxis***, ***should be*** **given** ***within*** **14 days** of **exposure** to the **hepatitis B virus** and **hepatitis B vaccination** is ***initiated*** at the **time** of the ***initial*** **HBIG** ***administration***.

Rabies Immunoglobulin (RIG) (Imogam® Rabies-HT) (HyperRAB® S/D)

- **RIG** is ***used*** in ***suspected*** of **exposure** to **rabies** as **20 IU/kg**, ***infiltrate*** **locally** ***around*** **bite**.
- It is **given** ***after*** the **wound** is ***cleaned*** with **soap** and **water** or **providone-iodine** and is ***followed by*** a **course** of **rabies vaccine**.

Tetanus Immune Globulin (TIG) (HyperTET® S/D)

- **TIG** is an **antibodies** ***against*** **tetanus toxin**, **allergic reactions**; **anaphylaxis** *may* **occur**.

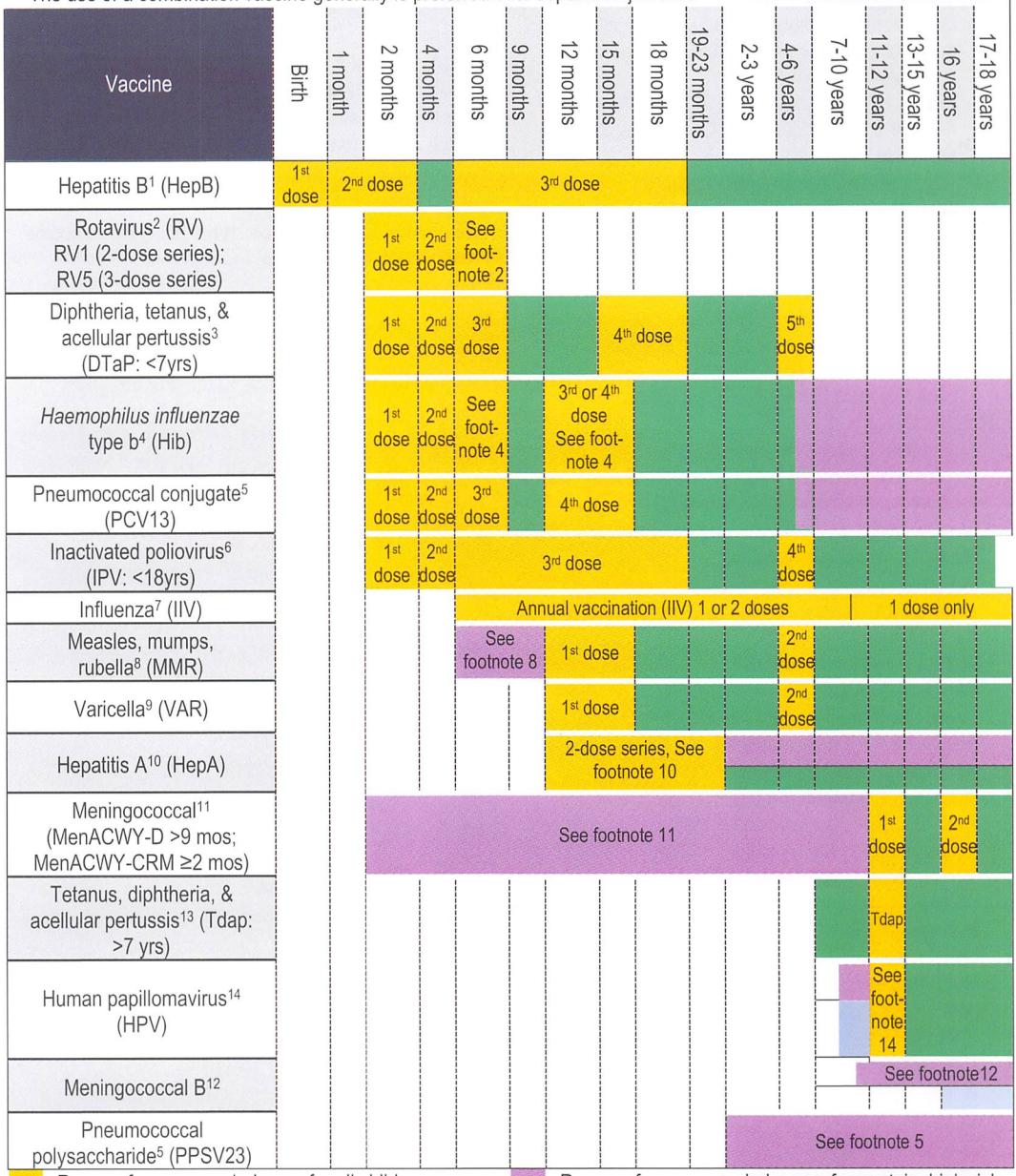
VZV (Varicella Zoster Virus) Immune Globulin (VariZIG®)

- **VZV Immune Globulin** is ***indicated*** for ***reducing*** the **severity** of **chicken pox** (**varicella zoster virus**) ***infections*** in ***high risk*** **individuals** ***after*** **exposure**.

Vaccination Schedule

2018 Vaccination Schedule; 0-18 Years of Aged

- The use of a combination vaccine generally is preferred over separate injections.



Range of recommended ages for all children

Range of recommended ages for catch-up immunization

No recommendation

Range of recommended ages for certain high-risk groups

Range of recommended ages for non-high-risk groups that may receive vaccine.

1) Hepatitis B (HepB) vaccine. (**min age: birth**)

Birth Dose (Monovalent HepB vaccine only):

- **Mother is HBsAg-Negative**: 1 dose within 24 hours of birth for medically stable infants >2,000 grams. Infants <2,000 grams administer 1 dose at chronological age 1 month or hospital discharge.
- **Mother is HBsAg-Positive**:
  - Give **HepB vaccine** and **0.5 mL of HBIG** (at separate anatomic sites) within 12 hours of birth, regardless of birth weight.
  - Test for HBsAg and anti-HBs at age 9–12 months. If HepB series is delayed, test 1–2 months after final dose.
- **Mother's HBsAg status is unknown**:
  - Give **HepB vaccine** within 12 hours of birth, regardless of birth weight.
  - For infants <2,000 grams, give **0.5 mL of HBIG** in addition to HepB vaccine within 12 hrs of birth.
  - Determine mother's HBsAg status as soon as possible. If mother is HBsAg-positive, give **0.5 mL of HBIG** to infants >2,000 grams as soon as possible, but no later than 7 days of age.

Routine Series:

- A complete series is 3 doses at 0, 1–2, and 6–18 months. (Monovalent HepB vaccine should be used for doses given before age 6 weeks.)
- Infants who did not receive a birth dose should begin the series as soon as feasible.
- Administration of **4 doses** is permitted when a combination vaccine containing HepB is used after the birth dose.
- **Minimum age** for the final (3rd or 4th) dose: 24 weeks.
- **Minimum Intervals**: Dose 1 to Dose 2: 4 weeks / Dose 2 to Dose 3: 8 weeks / Dose 1 to Dose 3: 16 weeks. (When 4 doses are given, substitute "Dose 4" for "Dose 3" in these calculations.)

Catch-up vaccination:

- Unvaccinated persons should complete a 3-dose series at 0, 1–2, and 6 months.
- Adolescents 11–15 years of age may use an alternative 2-dose schedule, with at least 4 months between doses (adult formulation **Recombivax HB®** only).

2) Rotavirus vaccines. (**minimum age: 6 weeks**)

Routine vaccination:

Rotarix®: 2-dose series at 2 and 4 months.

RotaTeq®: 3-dose series at 2, 4, and 6 months.

If any dose in the series is either **RotaTeq®** or unknown, default to 3-dose series.

Catch-up vaccination:

- Do not start the series on or after age 15 weeks, 0 days.
- The maximum age for the final dose is 8 months, 0 days.

3) Diphtheria, tetanus, and acellular pertussis (DTaP) vaccine. (**minimum age: 6 weeks** [**4 years** for **Kinrix®** or **Quadracel®**])

Routine vaccination:

- 5-dose series at 2, 4, 6, and 15–18 months, and 4–6 years.
  - **Prospectively**: A 4th dose may be given as early as age 12 months if at least 6 months have elapsed since the 3rd dose.
  - **Retrospectively**: A 4th dose that was inadvertently given as early as 12 months may be counted if at least 4 months have elapsed since the 3rd dose.

Catch-up vaccination:

- The 5th dose is not necessary if the 4th dose was administered at 4 years or older.

4) *Haemophilus influenzae* type b (Hib) vaccine. (**minimum age: 6 weeks**)

Routine vaccination:

- **ActHIB®**, **Hiberix®**, or **Pentacel®**: 4-dose series at 2, 4, 6, and 12–15 months.
- **PedvaxHIB®**: 3-dose series at 2, 4 & 12–15 months.

Catch-up vaccination:

- 1st dose at 7–11 months: Give 2nd dose at least 4 weeks later and 3rd (final) dose at 12–15 months or 8 weeks after 2nd dose (whichever is later).
- 1st dose at 12–14 months: Give 2nd (final) dose at least 8 weeks after 1st dose.
- 1st dose before 12 months and 2nd dose before 15 months: Give 3rd (final) dose 8 weeks after 2nd dose.
- 2 doses of PedvaxHIB® before 12 months: Give 3rd (final) dose at 12–59 months and at least 8 weeks after 2nd dose.
- Unvaccinated at 15–59 months: 1 dose.

5) Pneumococcal vaccines. (**minimum age: 6 weeks** [**PCV13**], **2 years** [**PPSV23**])

Routine vaccination with PCV13:

- 4-dose series at 2, 4, 6, and 12–15 months.

Catch-up vaccination with PCV13:

- 1 dose for healthy children aged 24–59 months with any incomplete* PCV13 schedule.

6) Inactivated poliovirus vaccine (IPV). (**minimum age: 6 weeks**)

Routine vaccination:

- 4-dose series at ages 2, 4, 6–18 months, and 4–6 years. Administer the final dose on or after the 4th birthday and at least 6 months after previous dose.

Catch-up vaccination:

- In the first 6 months of life, use minimum ages and intervals only for travel to a polio-endemic region or during an outbreak.
- If 4 or more doses were given before the 4th birthday, give 1 more dose at age 4–6 years and at least 6 months after the previous dose.

- A 4th dose is not necessary if the 3rd dose was given on or after the 4th birthday and at least 6 months after the previous dose.
- IPV is not routinely recommended for U.S. residents 18 years and older.

7) Influenza vaccines. (minimum age: 6 months)

Routine vaccination:

- Administer an age-appropriate formulation and dose of influenza vaccine annually.
  - Children 6 months–8 years who did not receive at least 2 doses of influenza vaccine; should receive 2 doses separated by at least 4 weeks.
  - Persons 9 years and older 1 dose.

8) Measles, mumps, and rubella (MMR) vaccine. (minimum age: 12 months for routine vaccination)

Routine vaccination:

- 2-dose series at 12–15 months and 4–6 years.
- The 2nd dose may be given as early as 4 weeks after the 1st dose.

Catch-up vaccination:

- Unvaccinated children and adolescents: 2 doses at least 4 weeks apart.

International travel:

- **Infants 6–11 months**: 1 dose before departure. Revaccinate with 2 doses at 12–15 months (12 months for children in high-risk areas) and 2nd dose as early as 4 weeks later.
- **Unvaccinated children 12 months and older**: 2 doses at least 4 weeks apart before departure.

9) Varicella (VAR) vaccine. (minimum age: 12 mo)

Routine vaccination:

- 2-dose series: 12–15 months and 4–6 years.
- The 2nd dose may be given as early as 3 months after the 1st dose (a dose given after a 4-week interval may be counted).

10) Hepatitis A (HepA) vaccine. (min. age: 12 mo)

Routine vaccination:

- 2 doses, separated by 6-18 months, between the 1st and 2nd birthdays. (A series begun before the 2nd birthday should be completed even if the child turns 2 before the second dose is given.)

Catch-up vaccination:

- Anyone 2 years of age or older may receive HepA vaccine if desired. Minimum interval between doses is 6 months.

11) Serogroup A, C, W, Y meningococcal vaccines. (Minimum age: 2 months [Menveo®], 9 months [Menactra®].

Routine vaccination:

- 2-dose series: 11-12 years and 16 years.

Catch-up vaccination:

- **Age 13-15 years**: 1 dose now and booster at age 16-18 years. Minimum interval 8 weeks.
- **Age 16-18 years**: 1 dose.

12) Serogroup B meningococcal vaccines (min age: 10 yrs [Bexsero®, Trumenba®]

Clinical discretion: Adolescents not at increased risk for meningococcal B infection who want MenB vaccine.

MenB vaccines may be given at clinical discretion to adolescents 16–23 years (preferred age 16–18 years) who are not at increased risk.

- **Bexsero®**: 2 doses at least 1 month apart.
- **Trumenba®**: 2 doses at least 6 months apart. If the 2nd dose is given earlier than 6 months, give a 3rd dose at least 4 months after the 2nd.

13) Tetanus, diphtheria, and acellular pertussis (Tdap) vaccine. (minimum age: 11 years for routine vaccinations, 7 years for catch-up vaccination)

Routine vaccination:

- **Adolescents 11–12 years of age**: 1 dose.
- **Pregnant adolescents**: 1 dose during each pregnancy (preferably during the early part of gestational weeks 27–36).

Catch-up vaccination:

- **Adolescents 13–18 who have not received Tdap**: 1 dose, followed by Td booster every 10y
- **Persons aged 7–18 years not fully immunized with DTaP**: 1 dose of Tdap as part of the catch-up series (preferably the first dose). If add doses are needed, use Td.
- **Children 7–10 years** who receive Tdap inadvertently or as part of the catch-up series may receive routine Tdap dose at 11–12 y.
- **DTaP inadvertently given after the 7th birthday**:
  - **Child 7–10**: DTaP may count as part of catch-up series. Routine Tdap dose at 11-12 may be given.
  - **Adolescent 11–18**: Count dose of DTaP as the adolescent Tdap booster.

14) Human papillomavirus (HPV) vaccine (minimum age: 9 years)

Routine and catch-up vaccination:

- Routine vaccination for all adolescents at 11–12 years (can start at age 9) and through age 18 if not previously adequately vaccinated. Number of doses dependent on age at initial vaccination:
  - **Age 9–14 years at initiation**: 2-dose series at 0 and 6–12 months. Minimum interval: 5 months (repeat a dose given too soon at least 12 weeks after the invalid dose and at least 5 months after the 1st dose).
  - **Age 15 years or older at initiation**: 3-dose series at 0, 1–2 months, and 6 months. Minimum intervals: 4 weeks between 1st and 2nd dose; 12 weeks between 2nd and 3rd dose; 5 months between 1st and 3rd dose (repeat dose(s) given too soon at or after the minimum interval since the most recent dose).

R; Advisory Committee on Immunization Practices (www.cdc.gov/vaccines/acip)

Hematopoietic Drugs

A) Drugs for Anemia

Erythropoietin

Iron Supplements

Folic Acid

Vitamin B_{12}

Drugs for Sickle Cell Disease

Erythropoiesis-Stimulating Agents (ESAs)

Epoetin alfa (Epiao®)# (Eprex®)#	**Epoetin beta** (NeoRecormon®)#
Darbepoetin alfa (Aranesp®)#	
Methoxy polyethylene glycol-epoetin beta (Mircera®)#	

Erythropoietin (**EPO**); is a ***glycoprotein hormone*** that ***controls*** **erythropoiesis** (*RBCs production*).

- **Peri-tubular cells** in the **kidneys** ***work as*** **sensors** that ***respond*** to **hypoxia** and ***mediate*** **synthesis** and **release** of **EPO**.

Recombinant **human erythropoietin**; **rhEPO** (**Epoetin alfa**, **Epoetin beta** and **Darbepoetin alfa**), *produced by* **recombinant DNA technology**.

- **Darbepoetin** is a ***modified form*** of **Erythropoietin** that is ***more heavily*** **glycosylated** with ***long-acting*** and ***delayed*** **onset of action** (half-life about three times that of epoetin alfa, it have no value in acute treatment of anemia).
- **Methoxy polyethylene glycol-epoetin beta**; is an ***isoform*** of **Erythropoietin** covalently attached to a long polyethylene glycol polymer with ***longer*** **half-life**.
- ***Administration*** (IV and SC).
  - **Epoetin alfa**; three times a week.
  - **Darbepoetin**; weekly.
  - **Methoxy polyethylene glycol-epoetin beta**; 2-week or monthly intervals.

Uses; **Anemia** ***associated with***; **end-stage renal disease** (not cleared by dialysis), **HIV**, **bone marrow disorders**, **prematurity** and **cancer**.

- ***Supplementation*** with **iron** may be *required to* ***ensure*** an **adequate response**.
- ***Dosages*** are ***adjusted*** to ***maintain*** a **target hemoglobin** up to, ***but not exceeding***, 10–12 g/dL (usually observed in about 10 days and an increase in hematocrit and hemoglobin levels in 2–6 weeks).
- ***Most common side effects***; **hypertension** and **thrombotic complications**.

FDA warning; in March 2007, the FDA issued a warning that **patients** ***with*** **chronic renal failure** or **cancer** whose ***serum*** **hemoglobin** is *raised to* ***more than*** **12 g/dL** ***with an*** **rhEPO** have ***greater*** **risk** of a **thrombotic event** **or**, in ***patients*** with ***advanced*** **head** and **neck cancers**, ***faster*** **tumor growth**.

Iron Supplements

- **Iron** is ***stored mostly*** in the **liver** as **ferritin** (iron-protein complex) *until needed by* the **body**, **iron** is ***delivered*** to the **marrow** for **hemoglobin production** by a ***transport*** **protein**, ***namely*** **transferrin**.
- **Iron deficiency anemia** (**IDA**) ***results from*** **acute** or **chronic blood loss**, from ***insufficient*** **intake** *during* periods of ***accelerated growth*** in **children**, and in ***heavily*** **menstruating** or **pregnant women**.
- **Iron** can be ***supplemented by*** the oral route or parenteral route;

Oral Iron Formulations

Ferrous Sulfate	Ferrous Gluconate	Ferrous Fumarate
Polysaccharide-iron Complex	Carbonyl Iron	

- A ***wide variety*** of **oral iron preparations** is ***available***.
- Because **Ferrous Iron** is ***most efficiently*** **absorbed**, **ferrous salts** ***should be used***.
- **Ferrous Sulfate**, **Ferrous Gluconate** and **Ferrous Fumarate** are ***all effective*** and ***inexpensive*** and are ***recommended for*** **most patients**.
- ***Pharmacokinetics***:
  - **Absorption**; **acidic conditions** in the **stomach** *keep* **iron** in the **reduced Ferrous** form, which is the ***more soluble*** (if iron stores are adequate, less will be absorbed).
  - *About* **50-100 mg** of **iron** can be ***incorporated*** into **hemoglobin daily**, ***but*** only ***about*** **25%** of **oral ferrous iron salt** can be **absorbed**.
- **Centers for disease control and prevention** (**CDC**) ***recommendations***;
  - *For* **infants**; 2-4 mg/kg/day of iron drops.
  - *For* **school-age children** and **adolescent boys**; 60 mg/day of iron.
  - *For* **adults**, **adolescent girls** and **pregnancy**; 60-120 mg/day of iron.
  - *For* ***primary prevention*** during **pregnancy**; 30 mg/day of iron.
- ***Repeat*** the **anemia screening** in ***after*** **4 weeks** of **iron supplements** → ***increase*** in **Hb concentration** of *greater than* or *equal* to **1 g/dL** → **iron-deficiency anemia** is ***confirmed***, ***continue*** **iron treatment** for **2 more months**, then ***recheck*** **Hb concentration** or **Hct** (***usually*** **3–6 months**).

Common side effects; (*dose-related*); **GI disturbances** *caused by local irritation* (**nausea**, **abdominal cramps**, **constipation** {if astringent} or **diarrhea** {*if irritant*}) and **dark stools** (Some patients have less severe GI side effects with one iron salt than another).

Drug Interactions;
- **Iron** ***reduce*** **absorption of Levothyroxine**.
- **Iron** ***reduce amount of*** **Levodopa** & **Methyldopa** *available to the body*.
- **Proton pump inhibitors** ***reduce*** **iron absorption** (*reduce the acidity*).

Lactoferrin (Pravotin®)#

- **Lactoferrin** (**LF**) is ***one of*** the **transferrin proteins** that ***transfer*** **Iron** to the **cells** and ***control*** the ***level*** of ***free*** **Iron** in the **blood**.
- **Lactoferrin** is ***widely represented*** in various ***secretory fluids*** (such as **milk**) and in **neutrophils**.
- It has **antimicrobial activity** (*decrease free iron for microbial growth*) and shows some **antiviral activity**. It has **anti-inflammatory**, **antioxidant** ***activity*** *and may* ***inhibits*** **growth** of **some cancers**.
- **Lactoferrin** can be ***purified*** from **milk** or ***produced*** **recombinantly**.

Administration of **30%** **Lactoferrin** ***saturated with*** **Iron** (*called* **Bovine Lactoferrin**) (**Pravotin®**) can ***used to*** correct **iron deficiency anemia** with ***less*** **GI side effects** (70% of product ***contain*** ***free*** **Lactoferrin** can ***correct excess*** ***free*** **Iron** and ***decrease*** ***free*** **Iron** **GI side effects**) than ***other traditional*** **Iron salts**.

Parenteral Iron Formulations

Iron Dextran (CosmoFer®)#	**Iron Sucrose** (Venofer®)#
Sodium Ferric Gluconate Complex (Ferrlecit®)#	**Ferumoxytol** (Feraheme®)#
Iron Carboxymaltose (Ferinject®)#	**Iron Isomaltoside -1000** (Monofer®)#

- **Parenteral iron *should be reserved for* patients** with **iron deficiency** *who are*;
  - * ***Unable to* tolerate oral iron.**
  - * ***Unable to* absorb oral iron.**
  - * ***Extensive* chronic anemia** (such as **chronic kidney disease**).
- **Parenteral administration *treats* IDA *rapidly*, *but produces* serious dose dependent toxicity.**

Iron Dextran (low-and-high-molecular weight) can be given by **deep IM or IV infusion** (IV is most commonly due to local pain and tissue staining that occur with the IM), *due to* ***risk of*** a **hypersensitivity** reaction *with* **Iron Dextran**, **allergy test *should be* confirmed *before* administration.**

Sodium Ferric Gluconate Complex and **Iron Sucrose** are ***given only*** by the **IV route**. They appear to be ***less likely*** to cause **hypersensitivity reactions** (due to high-molecular-weight).

- ***Dose calculation***; Volume of product required (mL) = [weight (kg) x (14 - Actual Hb) x (2.145)]/C
  - Where C= concentration of elemental iron (mg/ml) in the product being used:
  - Iron dextran: 50 mg/mL. Iron sucrose: 20 mg/mL. Ferric gluconate: 12.5 mg/mL
- ***Chronic use*** of **parenteral iron**, it is important to ***monitor* iron storage *levels*** to ***avoid*** the **serious toxicity *associated with* iron overload.**
- ***Side effects*** of ***IV* Iron Dextran *therapy***; **headache, fever, arthralgias, nausea** and **vomiting, back pain, flushing, urticaria, bronchospasm**, and **rarely anaphylaxis** and **death.**

- ***Newer iron complexes***; can be *administered at* ***much* higher doses *than*** the **older complexes** with ***very low levels*** of **free iron** (low incidence to iron overload or toxicity) and ***do not require* test doses.**

Ferumoxytol;
- It was specifically *designed to* **reduce immunological reactivity** (***no allergy test***).
- It can be ***rapidly*** *administered* (IV rate of **30–60 seconds**) as a 510 mg dose with the **second IV injection** administered 2 to 8 days later.

Ferric Carboxymaltose;
- It is a ***newer formulation*** of **parenteral iron** which is ***consists of*** a **ferric hydroxide core *stabilized by*** a **carbohydrate shell**, allows for ***controlled delivery*** of **iron** to **target tissues.**
- **Dose**; **15 mg/kg IV *up to* 1000 mg** may *repeat* **weakly**.
- ***Minimum* administration time**; </=15 minutes.
- ***Repeated weekly***; **not result** in ***accumulation*** in patients.
- ***No* allergy test.**

Iron Isomaltoside;
- It is a ***newer formulation*** of **parenteral iron** that has a **matrix structure** that *results in* ***very low levels*** of **free iron** and **labile iron.**
- **Dose**; ***higher doses*, 20 mg/kg** in a ***single visit*** (can cause iron correction in a single visit), ***may repeat* once** after **weak** (based on clinical judgement).
- ***Minimum* administration time**;
- **IV infusion**; ≤ 1000mg > 15 minutes - > 1000mg ≥ 30 minutes
- **IV injection**; 500 mg over 2 minutes.

Acute Iron Toxicity

- *Acute ingestion* of **10 tablets** of any commonly **oral iron preparations** can be *lethal* in **young children**;
  - **Necrotizing gastroenteritis**, with **vomiting**, **abdominal pain** and **bloody diarrhea** *followed by* **shock**, **lethargy** and **dyspnea**.
- ***Urgent treatment*** is **necessary**; **Whole bowel irrigation** and *administration* of **iron-chelating agent** such as **Deferoxamine** (***N.B.***; Activated charcoal does not bind iron and thus is ineffective).

Chronic Iron Toxicity (Iron Overload)

- It is also known as **hemochromatosis**; results when ***excess iron*** is ***deposited*** in the **heart**, **liver**, **pancreas** and **other organs**. It can lead to **organ failure** and **death**.
- It ***most commonly*** occurs in **thalassemia**.
- ***Clinical manifestations***;
  - Liver disease (hepatomegaly, 13%, cirrhosis 13%).
  - Skin bronzing or hyperpigmentation (70%).
  - Amenorrhea, impotence, hypogonadism.
  - Arthropathy, osteopenia and osteoporosis.
  - Diabetes mellitus (48%).
  - Cardiomyopathy.
  - Hair loss.
  - Koilonychia (spoon nails).
- ***Treatments***; the goal of therapy is to remove the iron before it can produce irreversible parenchymal damage;
  1) **Phlebotomy**; Once diagnosed blood is removed (phlebotomy), weekly phlebotomy; 7 mL/kg/phlebotomy (not to exceed 550 mL).
  2) **Chelation therapy**; In patients with hemochromatosis and heart disease, anemia, or poor venous access.
  3) **Surgical procedures**; In end-stage liver disease & severe arthropathy.

Iron Chelation Therapy

- ***Chelation therapy***; is a **medical procedure** that involves the ***administration*** of ***chelating agents*** to ***remove*** **heavy metals** ***from the*** **body**.
- ***Most common forms*** of **heavy metal** intoxication; **iron**, **lead**, **arsenic**, **copper** or **mercury**.

Deferoxamine (Desferal®)#

- **Deferoxamine** is a ***parenteral iron chelator***.
- It acts by ***binding*** **free iron** in **bloodstream** and ***enhancing*** its ***elimination*** in the **urine**.
- ***Administration***; Parenteral (IV, IM or SC).
- ***Affinity***; *theoretically*, **100 parts** by weight of **Deferoxamine** is capable of ***binding approximately*** **8.5 parts** by weight of **ferric iron**.
- ***Contraindication***; **severe renal disease** or **anuria** (excreted primarily by kidney).

Deferiprone (Ferriprox®)#

- **Deferiprone** is an ***oral iron chelator***.
- ***Administration***; Oral (3 times a day).
- ***Affinity***; **3 molecules** of **Deferiprone** are ***capable of*** **binding** to **1 atom** of **Iron**.
- ***Warning***; **Deferiprone** ***may cause*** **fatal agranulocytosis**.

Deferasirox (Exjade®)#

- **Deferasirox** is an ***oral iron chelator***.
- ***Administration***; Oral (once daily).
- ***Affinity***; ***2 molecules*** of **Deferasirox** are ***capable of*** **binding** to **1 atom** of **Iron** which are subsequently ***eliminated by*** **faecal excretion**.
- ***Warning***; ***may cause*** **severe** and *sometimes* **fatal kidney problems** or **liver problems**.

Vitamin B_{12} Supplements

- Vitamin B_{12} ***serves as*** a **cofactor** for ***several essential*** **biochemical reactions**.
- **Intrinsic factor**, a protein *secreted by* the **stomach** that is *required for* **gastrointestinal uptake** of dietary **vitamin B_{12}**.
- ***Deficiency of*** **Vitamin B_{12}** ***leads to*** **megaloblastic anemia**, **gastrointestinal symptoms** and **neurologic abnormalities** (tingling "pins and needles" in the hands & feet).
- ***Initial therapy*** **100–1000 mcg** of **vitamin B_{12} IM every other day** for **1–2 weeks** to ***replenish*** **body stores**. ***Maintenance therapy***; of **100–1000 mcg** of **vitamin B_{12}** IM ***once*** a **month for life**.
- ***Various*** **organic groups** may be ***covalently*** **bound** to the **cobalt atom**, *forming different* **cobalamins**; *such as* **Cyanocobalamin**, **Hydroxocobalamin** and **Methylcobalamin**.

Cyanocobalamin (Betolvex®)#

- **Cyanocobalamin** is a **Vitamin B_{12}** **prodrug**.

It is ***available***; **oral tablets**, **sublingual**, **parenteral** (**IM** and **SC**, not given IV due to it results in more rapid excretion) and **nasal spray** (Naso-cyanocobalamin®).

It is the ***cheapest price of all*** and it is the ***most widely used*** *form of* **Vitamin B_{12}**.

Due to it is ***rapidly excreted*** into the **urine**, it is also available in the ***protein-bound formulation*** such as **Cyanocobalamin Zinc Tannate** (Betolvex®) to ***improve*** **Cyanocobalamin kinetics**.

Cyanocobalamin is ***converted to*** the **active form**, "**Methylcobalamin**" by **glutathione** and **other enzymes** and **co-factors**, ***much higher dose*** of **Cyanocobalamin** may cause **cyanide toxicity** (*due to depletion of glutathione*) ***especially*** in **renal failure patients**.

In cases of **cyanide poisoning** the **patient** is ***given*** **Hydroxocobalamin**, which is a ***precursor to*** **Cyanocobalamin**.

- A ***very serious allergic reaction*** to **Cyanocobalamin** is ***rare***.

Hydroxocobalamin (Depovit-B_{12}®)#

- **Hydroxocobalamin** is ***another*** **Vitamin B_{12}** **prodrug**.

It is ***available***; ***only*** **parenterally** (**IM**), **IV** ***only used*** *for* **cyanide poisoning**, *dose 5 g infusion in 15 min.*

It is ***preferred*** than **Cyanocobalamin** ***because*** it is ***rapid response*** and ***more highly*** **protein-bound** and therefore has ***longer half-life***.

Hydroxocobalamin has also been used in the ***treatment*** of **cyanide poisoning**. **Cyanide** ***displaces*** the **hydroxo** ligand forming a ***stable*** **Cyanocobalamin**.

Methylcobalamin or Mecobalamin (Methycobal®)#

Methylcobalamin is the ***active form*** of **Vitamin B_{12}**.

Methylcobalamin is ***produced from*** **Cyanocobalamin**.

It is ***available***; **oral tablets**, **sublingual**, **parenteral** (**IM** or **IV**) and **nasal spray**.

It has ***higher*** **bioavailability** (***better absorbed***).

It has a ***longer retention*** in **tissues** (*only one third of its dose is excreted*).

Methylcobalamin is the ***only form*** of **Vitamin B_{12}** that ***can cross*** the **blood-brain barrier** ***without*** **assistance** or **conversion**;

  - Its **methyl group** ***stimulates*** **Serotonin** ***production*** in **CNS** (**mood support**).
  - ***High doses*** of **Methylcobalamin** have also been used to ***effective*** in **multiple sclerosis**.

Folic Acid (Folate) Supplements

- **Humans** ***cannot make*** **folates**; *therefore*, **Folic acid** (**Vitamin B_9**) has to be ***supplied*** through the **diet**. The **human body** ***needs*** **folate** to ***make*** **DNA**, ***repair*** **DNA** and ***methylate*** **DNA** as well as to act as a **cofactor** in ***certain*** **biological reactions**.

Folate deficiency (***megaloblastic anemia***) may be *caused by*;

1) **Increased demand** (*pregnancy and lactation*).
2) **Poor absorption** (*disorder in small intestine*).
3) **Alcoholism**.
4) **Drugs that are dihydrofolate reductase inhibitors** (**Methotrexate**, **Pyrimethamine** and **Trimethoprim**).

- **Folic acid** is an ***oxidized form***, it must be ***converted to*** **active form Tetrahydrofolate** (**Tetrahydrofolic acid**) in the ***body*** by **dihydrofolate reductase (DHFR)** ***enzyme***.
- ***Notes***;

Folic acid intake ***during*** **pregnancy** has been ***linked to*** a ***decrease*** **risk** of **neural tube defects** (**spina bifida**) and some ***other specific*** **kinds** of **birth defects**.

Folate is ***necessary for*** **fertility** in ***both*** **men** and **women**.

Folic acid appears to ***reduce*** the **risk** of **stroke** due to ***decrease*** **homocysteine concentration**.

Folic acid supplementation ***may slightly increase*** the **risk** of **some cancers**.

Folic Acid

- **1mg** of **folic acid** ***orally daily*** is **typically sufficient** to ***reverse*** **megaloblastic anemia** (it may administrated parenterally; IM, SC and IV).
- ***Usual adult dose for*** **folic acid deficiency**; **400-800 mcg**.

WARNING; **Folic acid** ***should not*** be **given** ***alone*** in ***patients with*** **pernicious anemia** ***without*** **knowing whether** they also have a **Vitamin B_{12} deficiency**.

N.B.;

Patients with **iron overload** usually ***become*** **vitamin C deficient**, *because* **iron** ***oxidizes*** vitamin C, **vitamin C** in doses **> 200 mg** for **adults** may be given in ***divided doses***, starting ***after*** an **initial month** of ***regular treatment*** with ***iron chelator***.

Iron Binding Dendrimers; is a ***novel*** **iron(Fe^{3+})-selective chelator** capable of ***removing*** **dietary iron** *from the* **GIT** and ***preventing*** the *development of* **iron overload** typical of **haemochromatosis** and **thalassaemia**.

Cobalamins has been ***assigned to*** **pregnancy category C** by the FDA, ***do not*** **administer Cobalamins**, ***preserved*** with **Benzyl Alcohol** to **pregnant women** (**Benzyl Alcohol** has been ***associated with*** **serious adverse events** and **death**).

Large amounts of **Folic acid** (>1,000 µg/daily) can ***mask*** the **damaging effects** of **vitamin B_{12}** ***deficiency*** by ***correcting*** the **megaloblastic anemia** *caused by* **vitamin B_{12}** ***deficiency*** ***without*** **correcting** the **neurological damage** that *also occurs*.

Drugs for Sickle Cell Disease

Hydroxyurea (Hydrea®)#

It is an ***antineoplastic drug used in*** **polycythemia vera** & **essential thrombocythemia**
It is also ***used to reduce the rate*** of **painful attacks** in **sickle-cell disease**.
It is also ***used in*** **AIDS** (*due to antiretroviral properties*).
- ***In sickle cell disease***; **Hydroxyurea** ***increases*** **fetal hemoglobin levels**, thus ***diluting*** the **abnormal hemoglobin S (HbS)** (*this process takes several months*).
- ***Common serious side effects***; **bone marrow suppression** and **cutaneous vasculitis**.

Pentoxifylline (Trental®)#

Pentoxifylline is a ***methyl-xanthine derivative*** that ***inhibits*** **phosphodiesterase enzyme** and ***affects*** **blood rheology**. It has been called a "***rheologic modifier***"
It ***improves*** **blood flow** by ***increasing*** **erythrocyte** and **leukocyte** ***flexibility***. It also ***inhibits*** **platelet aggregation**.
It is ***used*** in the treatment of **peripheral vascular diseases** and in the **management of cerebrovascular insufficiency**.
It is ***used*** in patients with **intermittent claudication**.
It is ***also effective*** in **venous ulcer** with compression therapy.
- ***Dose***; 400 mg orally 3 times a day.

B) Myeloid Growth Factors

Granulocyte Colony–Stimulating Factors (G-CSF)

- **Granulocyte Colony–Stimulating Factors** (**G-CSF**); is a ***glycoprotein*** that ***stimulates*** the **bone marrow** to ***produce*** **granulocytes** and **stem cells** and ***release them into*** the **bloodstream**.

Filgrastim (Neupogen®) (Zarxio®) | Tbo-filgrastim (Granix®)

Peg-filgrastim (Neulasta®)

- **Filgrastim** is a ***granulocyte colony-stimulating factor*** (***G-CSF***) ***analog***.
- It is *produced by* ***recombinant*** **DNA technology**, **G-CSF** ***regulates*** the **production** of **neutrophils** *within the* **bone marrow**.
- **Tbo-filgrastim** have ***slight*** **structural differences** than **Filgrastim**, the pharmacokinetic, safety and efficacy ***don't significantly differ***.
- **Peg-filgrastim** (*linked to* polyethylene glycol) has a human ***half-life*** of **15-80 hours**, ***much longer than*** **Filgrastim** (**3-4 hours**).
- ***Indications***;
  - **Neutropenia** ***associated with*** **congenital neutropenia**, **cyclic neutropenia**, **myelodysplasia** and **aplastic anemia**.
  - ***Secondary prevention of*** **neutropenia** ***in patients undergoing*** **chemotherapy**.
  - **Mobilization of peripheral blood cells in** ***preparation for*** **stem cell transplantation**.
- ***Administration***; **Filgrastim**; IV or SC. **Tbo-filgrastim** and **Peg-filgrastim**; SC only.
- ***Serious side effects***; **serious allergic reactions**, **bone pain** & ***rarely*** **splenic rupture**.

Granulocyte Macrophage Colony-Stimulating Factor (GM-CSF)

Sargramostim (Leukine®)

- **Sargramostim** is a ***recombinant granulocyte macrophage colony-stimulating factor***.
- ***Indications***; ***similar to*** those of **G-CSF**, ***administration***; IV or SC.
- ***Most common side effects***; **Fever**, **arthralgia** and **myalgia**.

C) Megakaryocyte Growth Factors

- **Megakaryocyte Growth** *and* **Development Factor** (**MGDF**), also *known as* ***Thrombopoietin*** (***THPO***); is a **glycoprotein hormone** *produced by* the **liver** and **kidney** which ***regulates*** the ***production*** of **platelets** by *stimulating* **megakaryocytes**.

Oprelvekin (Neumega®)

- **Oprelvekin** is ***recombinant*** **interleukin eleven** (**IL-11**), is a **thrombopoietic growth factor** that ***increase*** **platelet production**.
- **IL-11** is a member of a family of **human growth factors** and is being ***produced*** in the **bone marrow**.
- ***Indications***; ***Prevention*** of **severe thrombocytopenia** & ***secondary prevention*** of **thrombocytopenia** ***in patients undergoing*** **chemotherapy**. ***Administration***; SC.
- ***Most common side effects***; **Fatigue**, **headache**, **dizziness**, **anemia**, **lung edema** and **arrhythmias**.

Romiplostim (Nplate®) | Eltrombopag (Promacta®)

- **Romiplostim** is an ***analog*** of **thrombopoietin**, ***approved for*** treatment **chronic idiopathic** (*immune*) **thrombocytopenic purpura** (**ITP**), ***administered*** **weekly** intervals via **SC injection**.
- **Eltrombopag** is an ***orally active small-molecule thrombopoietin-receptor agonist***, ***approved for*** treatment **chronic idiopathic** (*immune*) **thrombocytopenic purpura** (**ITP**).

Special Topics

Formula Feeding

Premature

- *For* **premature baby born** ***before*** **37 weeks** or **low birth weight [LBW]** (***less than*** **2.5 kg**).
  - Nestlé® Pre NAN®
  - Similac® NeoSure®
  - Ronalac® Premature
  - Bebelac® Premature
  - Wyeth® S-26® PDF GOLD
  - Aptamil® PDF (Post Discharge Formula)
  - Blemil® Plus Premature
  - Enfalac® Premature

0-6 Months (Stage 1)

- Nestlé® NAN® 1
- Bebelac® 1
- Similac® Advance®
- Celia® Expert 1
- Primavita® 1
- Aptamil® 1
- Wyeth® S-26® GOLD 1
- Hero Baby 1
- Liptomil® 1 and Liptomil® Plus 1
- Swisslac® 1

6-12 Months (Stage 2)

- Nestlé® NAN® 2
- Bebelac® 2
- Similac® Gain® Advance® 2
- Celia® Expert 2
- Primavita® 2
- Aptamil® 2
- Wyeth® S-26® Promil GOLD
- Hero Baby 2
- Liptomil® 2 and Liptomil® Plus 2
- Swisslac® 2

1-3 Years (Stage 3)

- Nestlé® NAN® 3 and NAN® 3 Comfortis
- Bebelac® 3
- Similac® Gain® Advance® 3
- Celia® Expert 3
- Primavita® 3
- Aptamil® 3
- Wyeth® S-26® Progress GOLD
- Hero Baby 3
- Liptomil® 3 and Liptomil® Plus 3
- Swisslac® 3

Hypoallergenic (HA) Formula (0-12 Months)

- **Hypoallergenic (HA) Infant Milk** is ***designed*** to ***reduce*** the **risk** of ***developing*** **allergy** to **cows' milk protein** (higher risk of allergy, in case of family history of allergic diseases).
- A child with an immediate reaction to cow's milk protein may develop symptoms like vomiting, diarrhea, mucous and/or blood in stools, and abdominal pain. Some children may also develop a rash, runny nose or difficulty breathing.
  - Neocate®
  - Wyeth® S-26® HA GOLD
  - Liptomil® Plus HA
  - Aptamil® HA 1 and Aptamil® HA 2
  - Hero Baby HA
  - Similac® Isomil® (soy proteins)

Lactose Free (LF) Formula (0-6 or 0-12 Months)

- **Lactose Free (LF)** is a **lactose-*free*** **milk** based formula for the ***dietary*** **management** of **babies** and **young children** who are ***intolerant*** to **lactose** or **sucrose**, or who are ***experiencing*** symptoms such as **acute diarrhea**, **gas** and **bloating** caused by **lactose intolerance**.
  - SMA® LF
  - Bebelac® FL
  - Hero Baby LF
  - Swisslac® LF
  - Aptamil® LF
  - Wyeth® S-26® LF
  - Liptomil® Plus LF
  - Nestlé® NAN® LF

Anti Regurgitation (AR) Formula (0-12 Months)

- **Anti Regurgitation (AR)** is ***suitable for*** **infants** ***experiencing*** **regurgitation** or **mild gastroesophageal reflux** (designed to thicken in the stomach).
  - **Bebelac® AR**
  - **Hero Baby AR**
  - **Swisslac® AR 1** and **Swisslac® AR 2**
  - **Wyeth® S-26® GOLD AR**
  - **Liptomil® Plus AR**

Others

- **Anti Constipation (AC)**; - **Ronalac AC**
- **Novalac IT** (Improved Transit)
- **Extra Care (EC)** or **Gentle** or **Comfort**; for more digestion
  - **Bebelac® EC**
  - **Novalac® AC** (Anti Colic)
  - **Nestlé® NAN® Comfort 1** and **Nestlé® NAN® Comfort 2**
  - **Hero Baby Digest**
  - **Similac® Total Comfort**

Most Common Child Doses

Fever

Age	Drug	Conc.	Dose
< 6 Months	**Paracetamol** Oral Drops	100mg/1mL	10-15 mg/kg/dose every 4-6hr OR 2 drops per kg every 4-6hr
≥ 6 Months	**Paracetamol** Syrup	250mg/5mL	10-15 mg/kg/dose every 4-6hr OR Weight/4 = mL every 4-6hr
	Ibuprofen Syrup	100mg/5mL	5-10 mg/kg/dose every 6-8hr OR 1/3 X Weight = mL every 6-8hr
≥ 3 years	**Diclofenac** Supp.	12.5mg - 25mg	2-3 mg/kg/day OR 1-2 Supp. 12.5mg per 10 kg/day

Antihistamines

< 1 Year	**Dimetindene** (Fenistil®) Drops	1mg/1mL	3-10 drops 3 times daily OR 1 drop/kg 2 times daily
1-3 years			10-15 drops 3 times daily
2-6 years	**Cetirizine** (Zyrtec®) Drops	10 mg/1mL	5 drops twice daily
	Cetirizine (Zyrtec®) Solution	1 mg/1mL	2.5 ml twice daily
≥ 3 Years	**Fexofenadine** (Telfast®) Susp	30mg/5mL	5 mL once daily

Antiemetic

0-12 years	**Ondansetron** (Zofran®) Amp	2 mg/1mL	0.1 mL/1 kg OR 1 mL/10 kg
0-12 years	Cortigen® B6 OR Cortiplex® B6	50 CU	1-2 Amp IM

Dermatology

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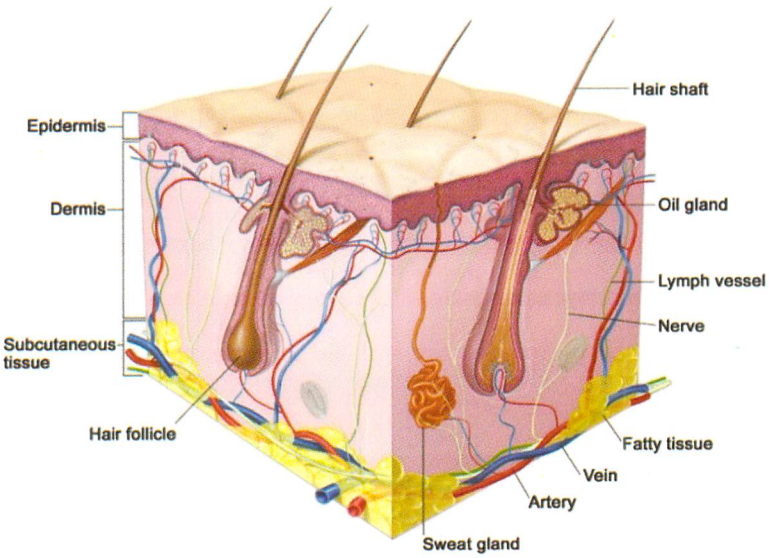


Acne Vulgaris (AV)

- Skin Layers:-

Epidermis

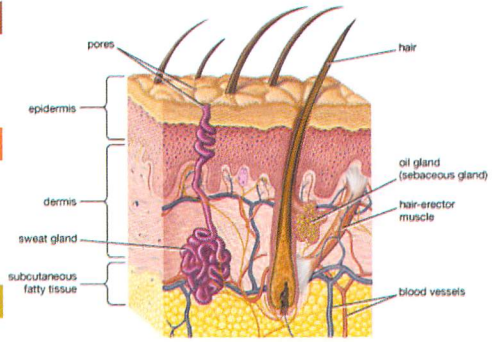
- ***Produce*** **keratin** (protect *against* harmful substances and control water released from the body).
- Also ***produce*** **melanin** which gives the skin color.

Dermis

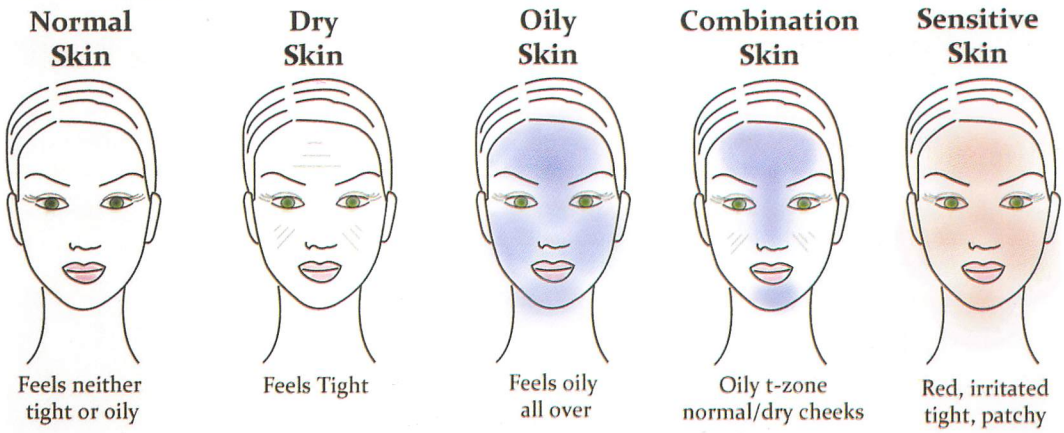
- Contain **sebaceous** and **sweat *glands***.
- The dermis is also composed of matrix components such as **collagen** (which provides strength) and **elastin** (which provides elasticity).

Subcutaneous Tissues

- Made up of **fat** (fat storage).



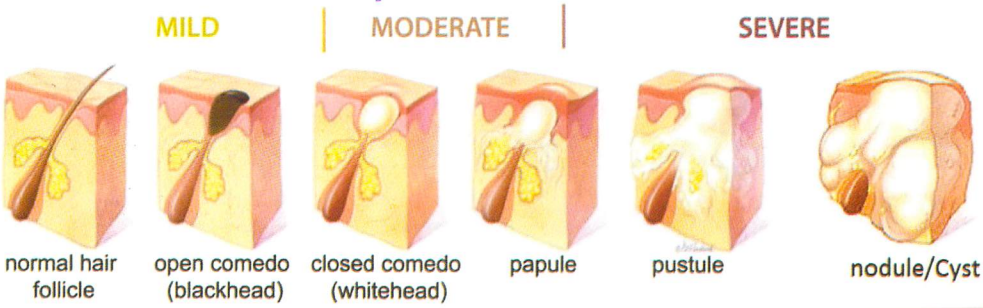
- Skin Types:-



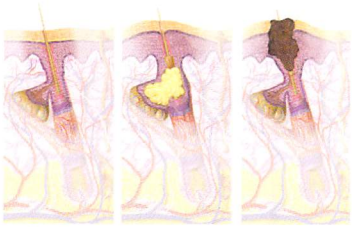
- Acne Definition:-

- **Acne Vulgaris** is a ***chronic*** **inflammatory skin disease** ***involving*** **blockage** and/or **inflammation** of **pilosebaceous units** (hair follicles and their accompanying sebaceous gland), ***characterized by presence*** of **open** or **closed comedones** (**blackheads** and **whiteheads**) and ***inflammatory*** **lesions**, ***including*** **papules**, **pustules** or **nodules** (**cysts**).

- Acne Forms and Severity:-



- ***Forms***;
  - **A) Non-inflammatory Lesions**;
    - * **Comedones** (**whiteheads** and **blackheads**);
      - A ***hard*** **plug**, caused by an ***accumulation*** of **keratin** and **oil** ***within*** the **hair follicle**.
      - A **comedo** can be ***open*** (**blackhead**) or ***closed*** by **skin** (**whitehead**),
      - **Occur** ***with*** or ***without*** **acne**.



  - **B) Inflammatory Lesions**;
    - * **Papules**; A ***small***, **solid**, *usually* **inflammatory** ***elevation*** of the **skin** that ***does not contain*** **pus**.
    - * **Pustules**; A ***small*** **inflamed** ***elevation*** of the **skin** that is ***filled with*** **pus**.
    - * **Nodules** (**Cysts**); - Is **morphologically** ***similar*** to a **papule**, but is ***greater than*** in **width** and **depth**, and ***most frequently*** **centered** in the **dermis** or **subcutaneous fat**.
      - **Large nodules** were ***previously*** *referred to as* **cysts**.
- ***Severity*** (***Grading***);
  - * **Grade I** (**Comedonal Acne**); *Presence of* **open** and **closed comedones** *but* ***usually no*** **inflammatory papules** or **nodules**.
  - * **Grade II** (**Mild Acne**); *Presence of* **comedones** and a ***few*** **papulopustules**.
  - * **Grade III** (**Moderate Acne**); *Presence of* **comedones**, ***inflammatory*** **papules** and **pustules** (a greater number of lesions are present than in milder inflammatory acne).
  - * **Grade IV** (**Nodulocystic Acne** or **Cystic Acne**); *Presence of* **comedones**, ***inflammatory*** **lesions**, and ***large*** **nodules** *greater than* **5 mm** in **diameter**; scarring is often evident (is a ***deep*** **infections** that are **nodule** or **cyst-like** and can ***become*** **large**).

Blackheads

Whiteheads

Papule

Pustule

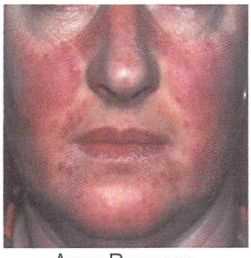
Nodule

Mild Acne

Moderate Acne

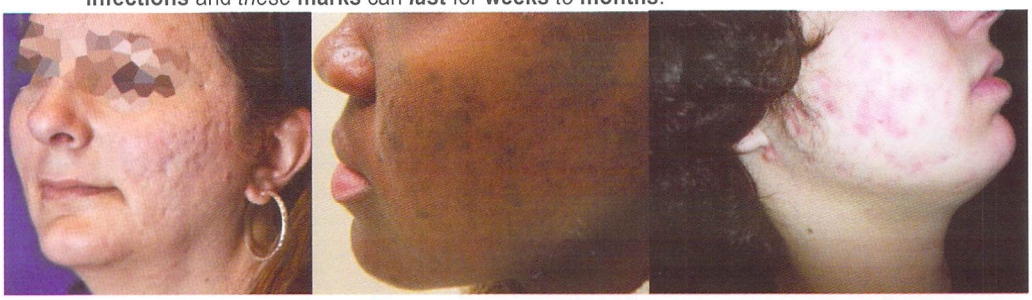
Nodulocystic Acne or Cystic Acne

- **Acne Rosacea**;
  - A ***combination*** of **rosacea** and **acne**.
  - **Rosacea** is ***characterized by*** *periodic* **redness** of the **skin**, *usually* on the **cheeks** and ***spreading*** *across* the **nose**.
  - In ***more advanced*** **cases** ***flare-ups*** occur, *followed by* **crusty skin** and ***excessive*** **flaking**.
  - The ***very*** **initial stage** of a **rosacea flare-up** *involves* ***release*** of ***inflammatory*** **"histamine"** *produced by* the **skin** → **redness**, **puffiness** and *sometimes* **itching** → ***production*** of **inflammatory skin "cytokines"** such as **interleukin-1**, **interleukin-6**, **interleukin-8**, **tumor necrosis factor-alpha** and **interferon-alpha** and ***collectively*** they ***produce*** a **full flare-up**.


Acne Rosacea

- Complications:-

- **Acne Scars**; are the ***result*** of **inflammation *within*** the **dermis** *brought on* by **acne** are ***usually*** **sharp-sided *depressions*** or ***pits***.
- **Acne Hyperpigmentation Spots**; This **inflammation *stimulates* specialized pigment-*producing* skin cells (melanocytes)** to ***produce*** *more* **melanin pigment** which ***leads to*** the **skin's darkened *appearance* (postinflammatory hyperpigmentation; PIH)**.
- **Acne Red Spots**; **People** *with* ***light*** **skin** usually ***develop*** **red** *to* **purple *marks*** *at the* **sites** of **infections** and *these* **marks** can ***last*** for **weeks** *to* **months**.



Acne scars **Acne Hyperpigmentation Spots** **Acne Red Spots**

- Etiology and Pathogenesis:-

- **Excess Sebum Production**; **Androgen hormones** (such as **Dihydrotestosterone**; **DHT**) ***promote*** **sebum *production*** and ***release*** in **boys** and **girls**.
- **Follicular Hyperkeratinization**; ***Increased*** **keratinocyte proliferation** & ***decreased*** **desquamation (slough off)**, leading to **sebum-** and **keratin-*filled* microcomedones** which can ***block*** **follicular canal**.
- ***Propionibacterium acnes*** (***P. acnes***) **Colonization**; ***P. acnes*** is a **Gram-positive anaerobic rod bacteria** that ***use*** **sebum, cellular debris** and **metabolic byproducts** from the ***surrounding*** **skin tissue** as their ***primary*** **sources** of **energy** and **nutrients**. ***P. acnes*** *produce* **bacterial lipases** (enzymes) that ***convert*** **sebum *into* free fatty acids**, which ***irritates*** the **follicle linings**, this **irritation** *causes* ***excessive*** **production** of **cells** and **cellular debris**, which ***blocks*** the **follicles** and **traps *P. acnes* inside**.
- **Essential Fatty Acids** (**Linoleic Acid**) **Deficiency**; - **Sebum *deficient*** in **linoleic acid** is **hard**, **sticky** and ***lacking*** in **anti-inflammatory *properties***.

- Acne Complicating Factors and Risk Factors:-

- **Genetic Factors**
- **Stress**
- **Coffee**
- **Wheat** and **Milk**
- **Zinc Deficiency**
- **Menses**
- **Hormones Changes**
- **Essential Fatty Acids Deficiency**
- **Oral Contraceptives**
- **Cosmetics**
- **Environmental Factor**
- **Sun Exposure**

Managements

[American Academy of Dermatology (AAD) Guidelines; 2016]

A) Diet

- ***High*** **glycemic index diets** may be ***associated*** with **acne** (strength of recommendation; B).
  - Low Glycemic Load (LGL) diet had significant improvement in acne severity, a significant reduction in weight and body mass index (BMI), a significant decrease in free androgen index, and improved insulin sensitivity.
- ***Certain*** **dairy products**, *especially* **skim milk**, *may* ***aggravate*** **acne** (strength of recommendation; B).
- ***Some*** **small preliminary studies** have ***examined*** the **role** of **antioxidants** (***including*** oral **zinc**), **probiotics** and **fish oil** on **acne**; evidence is not strong enough to support these.

B) Non-antibiotic Topical Therapies

Benzoyl Peroxide (BP) (PanOxyl®) - (Akneroxid®)

- **Benzoyl Peroxide** is **one** of the ***first-line* agents** in the **treatment** of **acne vulgaris**.
- **Dosing**; **2.5%, 5%,** or **10%** in **gel, wash** or **cream** (once or twice per day after skin cleaning).
- **Possible mechanism**; Kills *P. acnes* by oxidizing its proteins and may inhibiting inflammation.
- **Combinations**; May be **used** in **combination *with*** a **topical antibiotic** such as **Benzoyl peroxide/Clindamycin (BenzaClin® - Duac® - Onexton®)/ Benzoyl peroxide/ Erythromycin (Acne Benz® - Acnidu®)** OR **retinoid** such as **Benzoyl peroxide/Adapalene (Epiduo®)**.
- **Adverse effects**; **Hypersensitivity reactions, contact sensitization reactions** and **erythema**.
- **Pregnancy**; **category C**.

Tretinoin (Retin A®) - (Acne-Free®) - (Acnetin®) - (Eudyna®)

- **Tretinoin** is **one** of the ***first-line* agents used** in the **treatment** of **acne vulgaris**.
- **Dosing**; ***Apply*** a **thin layer** of **tretinoin *once* daily**, ***before* bedtime**, to **skin** *where* ***lesions* occur** [Keep away from eyes, mouth, nasal creases and mucous membranes]
- **Possible mechanism**; - They are structurally related to vitamin A.
  - Retinoids reduce inflammation, normalize the follicle cell life cycle, and reduce sebum production and inhibits microcomedone formation.
- **Adverse effects**; **Dry skin, peeling, scaling, flaking, burning sensation, erythema, pruritus, pain** of **skin, sunburn** and **hyper-/hypopigmentation**.

[Ultraviolet light and environmental exposures (wind and cold) can cause irritation and should be avoided]
- **Pregnancy**; **category C**.

Adapalene (Differin®)

- **Adapalene** is a ***topical* retinoid *used*** in **treatment** of **acne vulgaris** in **patient ≥ 12 years**.
- **Dosing**; ***Apply*** a **thin film** of **adapalene** to the ***entire* face** and ***any other* affected areas** of the **skin *once* daily** in the **evening**, *after* **washing *gently*** with a **non-medicated soap**.
- **Adverse effects**; **Erythema, scaling, dry skin, burning/stinging, skin discomfort, pruritus, sunburn, hypersensitivity, face/eyelid edema** and **lip swelling**.

[Use with caution, especially when using preparations containing sulfur, resorcinol, or salicylic acid]
[Ultraviolet light and environmental exposures (wind and cold) can cause irritation and should be avoided]
- **Pregnancy**; **category C**.

Tazarotene (Tazorac®)

- **Tazarotene** is a ***topical* retinoid *used*** in **treatment** of **acne vulgaris**.
- **Dosing**; ***Apply*** a **thin layer** of **tazarotene *only*** to the **affected area *once* daily** in the **evening**.
- **Contraindications**; **Pregnancy** and **hypersensitivity**.
- **Adverse effects**; **Pruritus, burning, skin redness, peeling, dry skin** and **erythema**.

[Avoid exposure to sunlight, sunlamps, and weather extremes]
- **Pregnancy**; **category X**.

Salicylic Acid 0.5-2%

- **Salicylic Acid** is **used *alone*** or in ***combination*** with ***other* drugs** for the ***symptomatic* treatment** of **acne**.
- **Dosing**; *Appropriate* **topical** preparations *containing* **salicylic acid 0.5-2%**.
- **Duration** of **therapy**; - ***Initially***; ***apply* once *daily*** then ***increase*** to **2-3 times daily**, *if necessary*
  - ***If* dryness** or **peeling *occurs*, *reduce* application** to **once daily** or ***every* other day**.
- **Possible mechanism**; Keratolytic properties.
- **Adverse effects**; **Hypersensitivity reactions, *excessive* erythema** and **scaling**.
- **Pregnancy**; **category C**.

Azelaic Acid (Azelex®) (Azaderm®)

- **Azelaic Acid** is a ***topical*** **treatment** of ***mild*** to ***moderate*** **inflammatory acne vulgaris**.
- **Dosing**; A ***thin*** **film** *should be* ***gently*** but *thoroughly* **massaged** ***into*** the ***affected*** **areas** ***twice*** **daily** (in the morning and evening).
- **Adverse effects**; **Pruritus**, **burning**, **stinging**, **tingling**, **erythema**, **dryness** and **peeling**.
- **Pregnancy**; **category B**.

Resorcinol/Salicylic Acid (Acnevir®)

- **Dosing**; - Cream, cloth, foam, or liquid cleansers 2%: use to clean face once or twice a day.
  - Gel 0.5% or 2%: apply small amount to face twice a day.
  - Pads 0.5% or 2%: use pad to cover affected area 1-3 times a day.
  - Patch 2%: use at bedtime, after washing face and allowing face to dry at least 5 min.
- **Contraindications**; **hypersensitivity** to **salicylic acid**.

C) Antibiotic Topical Therapies

Clindamycin (Cleocin T®) | Erythromycin (Aknemycin®)

- **Dosing**; ***Apply*** a **thin film** of **Erythromycin** (***once*** or ***twice*** **daily**) OR **Clindamycin** (***once*** **daily**) to the **skin** where **acne lesions** ***appear***.
- ***Not recommended*** as **monotherapy** ***because*** of the ***risk*** of **bacterial resistance**.
- **Duration** of **therapy**; ***Maintenance*** **therapy** ***needed*** to ***prevent*** **recurrence**.
- **Combinations**; - **Erythromycin** + **Benzoyl peroxide** (**Acne Benz®** - **Acnidu®**)
  - **Clindamycin** + **Benzoyl peroxide** (**BenzaClin®** - **Duac®** - **Onexton®**)
  - **Clindamycin** + **Tretinoin** (**Ziana®** - **Veltin®**)
- **Contraindications**; **hypersensitivity**.
- **Pregnancy**; **category B**.

Dapsone (Aczone®)

- **Dapsone** ***gel*** is used for the ***treatment*** of **acne vulgaris** in **patients** ≥ **12 years** of ***age***.
- **Dosing**; ***Apply*** a **thin layer** to the **acne** ***affected*** **area**, ***twice*** **daily**.
- **Duration**; If there is ***no*** **improvement** ***after*** **12 weeks**, **treatment** ***should be*** **reassessed**.
- **Adverse effects**; **Oiliness**, **peeling**, **dryness**, **erythema**, **burning** and **pruritus**.
- **Pregnancy**; **category C**.

Systemic Antibiotics

- ***Systemic*** **antibiotics** are ***indicated*** for use in ***moderate*** to ***severe*** ***inflammatory*** **acne** and ***should be*** **used** in ***combination*** with a ***topical*** **Retinoid** and **Benzoyl Peroxide** (**BP**).

Agent	Adult Dose	Duration
Tetracycline	- 1 g daily given in divided doses; when improvement occurs in 1-2 weeks, decrease slowly to a maintenance dosage of 125-500 mg daily.	until improvement
Minocycline	- 50 mg 1-3 times daily.	
Doxycycline	- 200 mg on the first day of treatment (administered 100 mg every 12 hours) followed by a maintenance dose of 100 mg/day.	
Amoxicillin	- 250 mg twice a day up to 500 mg 3 times a day.	
Cephalexin	- 500 mg twice a day.	

- **N.B.**; **Trimethoprim/Sulfamethoxazole**, **Trimethoprim**, **Erythromycin** and **Azithromycin** are ***not approved*** by the **US FDA** for ***treatment*** of **acne**, but they are ***use*** **off-label**.

Hormonal Agents

A) Combined Oral Contraceptive Pills (COCPs);

- **COCPs** can ***decrease*** the **production** of **androgen hormones** by the **ovaries**, ***resulting*** in ***lower*** **skin** ***production*** of **sebum**, and *consequently* ***reduce*** **acne severity**.
- ***Third-*** or ***fourth-generation*** **progestins** such as **Desogestrel**, **Drospirenone**, or **Norgestimate** are ***preferred*** for **women** ***with*** **acne** *due to* their ***stronger*** **antiandrogenic effects**.
- **COCPs** that are ***commonly*** **used**;
  - **Ethinyl Estradiol/Norgestimate** (**Cilest®**).
  - **Ethinyl Estradiol/Norethindrone Acetate/Ferrous Fumarate** (**Loestrin® Fe**).
  - **Ethinyl Estradiol/Drospirenone** (**Yasmin® - Yaz®**).
  - **Ethinyl Estradiol/Drospirenone/Levomefolate** (**Safyral®**).

B) Spironolactone (Aldactone®);

- It is an **aldosterone receptor** ***antagonist*** that *exhibits* ***potent*** **antiandrogen activity** by ***decreasing*** **testosterone** ***production*** and by ***competitively inhibiting*** **binding** of **testosterone** and **dihydrotestosterone** to **androgen receptors** in the **skin**.
- It is ***not*** **approved** by the **FDA** for the ***treatment*** of **acne**, but it is ***use*** **off-label**.

C) Flutamide (Eulexin®);

- It is a ***nonsteroidal*** **selective androgen receptor** ***blocker*** used in ***treatment*** of **prostate cancer**.
- It is ***not*** **approved** by the **FDA** for the ***treatment*** of **acne**.

D) Corticosteroids;

- **Prednisone** (Low daily dose), ***alone*** or ***with*** *high* **estrogen** ***containing*** **COCPs**, has *shown* ***efficacy*** in the **treatment** of **acne** and **seborrhea**.

Isotretinoin

Isotretinoin (Roaccutane®) (Accutane®)

- **Isotretinoin** is a ***form*** of **vitamin A**, **used** in **Recalcitrant Nodulocystic Acne** (**Severe Acne**). **Isotretinoin** ***decrease*** **sebum** ***production***, **acne** ***lesions*** and **acne** ***scarring***.
- **Dosing**; - *Severe*: **≥12 years of age: 0.5-1 mg/kg/day** ***orally*** in **2 divided doses** ***with*** **food**.
  - *Moderate*: **≥12 years of age: 0.3-0.5 mg/kg/day** ***orally*** in **2 divided doses** ***with*** **food**.
  - *Adults*: **0.5-1 mg/kg/day** ***orally*** in **2 divided doses** ***with*** **food**.
- **Duration** of **therapy**; **15-20 weeks**.
- **Contraindications**; ***Hypersensitivity*** to **Isotretinoin** or **Vitamin A** and **Pregnancy**.
- ***Most Common*** **Side Effects**; **Cheilitis** (90%), **Conjunctivitis** (40%), **Irritation** (40%), **Hypertriglyceridemia** (25%), **Bone & joint pain** and ***increase*** **liver enzymes** and **erythrocyte sedimentation rates** (**ESR**).
- **Baseline monitoring**; **Liver function test**, **pregnancy test** and **lipid panel**.
- **FDA Warning**; **Pregnancy category X**; **Teratogenic**; ***Must not*** be *used by* **women** and **adolescents** who are **pregnant** or who ***may become*** **pregnant**; **EXTREMELY HIGH** ***risk*** that **SEVERE birth defects**; **Prescribers** ***must*** **register** with **iPLEDGE**, an FDA-approved risk management program designed to minimize pregnancy exposures to isotretinoin; patients must be registered and meet all requirements of iPLEDGE.
- **Nursing**; ***Not yet determined***.
- **Pediatric**; ***Safety*** and ***effectiveness*** have ***not*** been ***established*** in **children <12 years** of **age**.

	Mild Acne	Moderate Acne	Severe Acne
1st line Treatment	Benzoyl peroxide (BP) OR Topical Retinoid OR Topical Combination Therapy [BP + Antibiotic OR BP + Retinoid OR BP + Antibiotic + Retinoid]	Topical Combination Therapy [BP + Antibiotic OR BP + Retinoid OR BP + Antibiotic + Retinoid] OR Oral antibiotic + Topical Retinoid + BP OR Oral antibiotic + Topical Retinoid + BP + Topical antibiotic	Oral antibiotic + Topical Combination Therapy [BP + Antibiotic OR BP + Retinoid OR BP + Antibiotic + Retinoid] OR Oral Isotretinoin
Alternative Treatment	Add topical retinoid OR BP (if not on already) OR Consider alternative retinoid OR Consider topical dapsone	Consider alternative combination therapy OR Consider change in oral antibiotic OR Add COCPs OR Spironolactone in females OR Consider oral Isotretinoin	Consider change in oral antibiotic OR Add COCPs OR Spironolactone in females OR Consider oral Isotretinoin

Treatment algorithm for the management of acne vulgaris in adolescents and young adults

Physical Modalities

Chemical Peels

- A **chemical peel** is a ***technique*** **used** to ***improve*** the ***appearance*** of the **skin** on the **face**, **neck** or **hands**.
- A **chemical solution** is ***applied to*** the **skin** that ***causes*** it to **exfoliate** and ***eventually*** **peel off**.
- The **new**, ***regenerated*** **skin** is *usually* **smoother** and ***less*** **wrinkled**.
- The **new skin** is also *temporarily* ***more*** **sensitive** to the **sun**.
- There are **3 basic types** of **chemical peels**:
  1) **Superficial** or **lunchtime Peel**; by using ***mild*** **acids** such as **Alpha-hydroxy Acid** (**AHA**) and **Salicylic Acid**; improve appearance of mild skin discoloration and rough skin as well as to refresh the skin.
  2) **Medium Peel**; by ***using*** **Glycolic** or **Trichloroacetic Acid** (**TCA**); improve age spots, fine lines and wrinkles, freckles and moderate skin discoloration.
  3) **Deep Peel**; by ***using*** **Trichloroacetic acid** (**TCA**) or **Phenol**; removes moderate lines, age spots, freckles and shallow scars. Patients will see a dramatic improvement in skin appearance.

Comedo Removal

- A **dermatologist** or **cosmetologist** may ***extract*** **blackheads** (open comedones) using ***gentle*** **pressure** ***around*** the **pore opening**, and **whiteheads** (closed comedones) by ***incision*** with a **large needle** or a **blade**.

Laser and Light Devices

- ***Some*** **laser** and **light devices** may be ***beneficial*** for **acne**.

Dermatitis

- Dry Skin *also known* as **Xerosis** [ze-ROW-sis] is a ***common*** **condition** that the **skin** ***loses*** *too* **much water** or **oil** → ***lose*** **moisture** and it *may* **crack** and **peel**.
- ***Extremely*** Dry Skin can be a ***warning*** **sign** of **Dermatitis** → ***inflammation*** of the **skin**.
- **Dermatitis** is a ***group*** of **skin conditions** that *includes*;

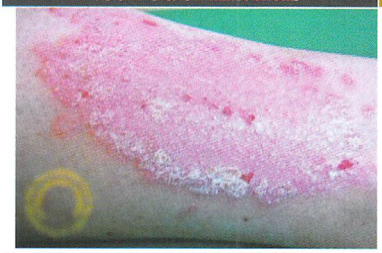
Contact Dermatitis

Contact dermatitis results from direct contact with certain substances called allergens
Common allergens include rubber, costume jewelry, perfume, cosmetics, hair dyes and poison ivy.

Atopic Dermatitis (Eczema)

Occurs in the folds of the elbows, backs of the knees or the front of the neck.
It tends to flare periodically and then subside for a time, even up to several years.

Neurodermatitis

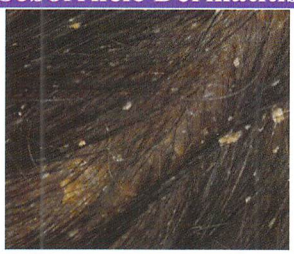


Neurodermatitis occurs because of repeated scratching.
Typicallyoccurs on the scalp, neck, wrist, upper forearm & ankle.

Perioral Dermatitis

usually affects the area around the mouth, but can also affect the areas around the nose, cheeks and eyes

Seborrheic Dermatitis



often found on oily areas of the body, such as the face, upper chest, back and scalp.

Atopic Dermatitis (Eczema)

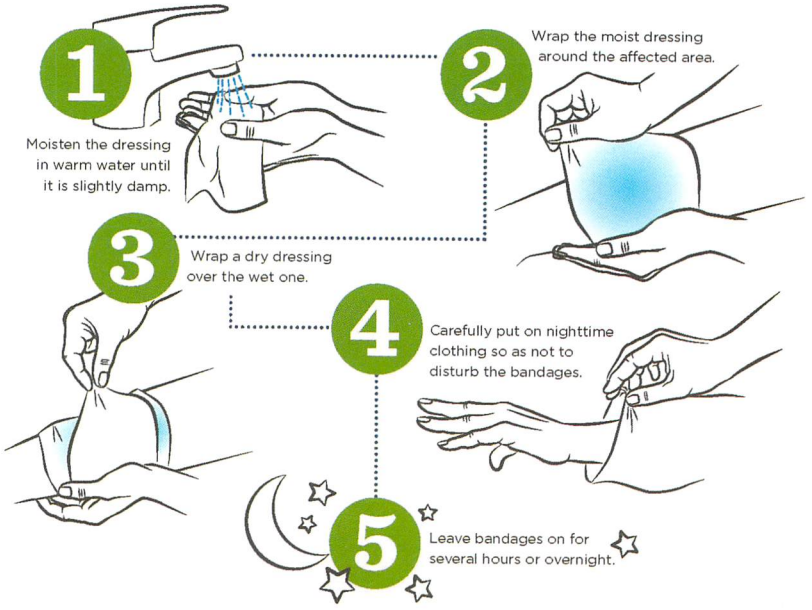
- **Atopic Dermatitis** (**AD**) [***popular name***; **Eczema**] is a ***chronic***, ***pruritic***, **inflammatory dermatosis** that ***affects*** *up to* **25%** of **children** and **2%** to **3%** of **adults**.
- **AD** ***onset*** is ***most common*** between **3** and **6 months** of **age**, with *approximately* **60%** of **patients** ***developing*** the *eruption* in the **first year** of **life** and **90%** by **5 years** of **age**.
- **Managements** (*recommendations*);
  - **A) Non-pharmacological Managements**;
    - 1) ***Use*** of **moisturizers** (Strength of recommendation; A); **Moisturizers** can be the ***main*** **primary** ***treatment*** for **mild disease** and **should be** ***part*** of the **regimen** *for* **moderate** and **severe disease**.
    - 2) **Bathing** and **bathing** ***practices*** (C); **Bathing** *with* **water** can **hydrate** the **skin** and ***remove*** **scale**, **crust**, **irritants**, and **allergens**, which can be *helpful for* **patients** with **AD**.

3) *Application* of **moisturizers** ***after*** **bathing** (B); to ***improve*** **skin hydration** and ***decrease*** **transepidermal water loss**.

4) ***Limited*** **use** of **non-soap cleansers** (C).

5) ***Against*** **use** of **bath** ***additives***, **acidic spring water** (C).

6) **Wet-Wrap Therapy** (B); **Wet-wrap therapy** (**WWT**) is **one method** to ***quickly reduce*** **AD severity**, and is often **used** in the ***setting*** of **significant flares** and/or **recalcitrant disease**.



B) Pharmacological Managements;

1) **Topical Corticosteroids** (**TCS**).

2) **Topical Calcineurin Inhibitors** (**TCI**); **Tacrolimus** (**Protopic®**) - **Pimecrolimus** (**Elidel®**).

3) **Topical Antimicrobials** and **Antiseptics**.

- *Staphylococcus aureus*, in particular, is a frequent culprit and colonizer of the skin in AD.
- Bleach (Clorox) baths and ***intranasal*** **Mupirocin** for those with ***moderate*** to ***severe*** **AD**.

4) **Topical Antihistamines**;

5) **Topical Phosphodiesterase Inhibitors**; **Crisaborole** (Eucrisa®) is approved in 2016 by the US FDA for the treatment of **mild-*to*-moderate AD** in **patients 2 years** of age and ***older***.

C) **Phototherapy**; **Phototherapy** is a ***second-line*** **treatment**, after failure of first-line treatment (emollients, topical steroids, and topical calcineurin inhibitors).

D) **Systemic Immunomodulating Medications**;

- **Cyclosporine**, **Methotrexate** (**MTX**), **Mycophenolate Mofetil** (**MMF**), and **Azathioprine** (**AZA**) are used the ***most*** and are ***more efficacious*** in the treatment of ***refractory*** **AD**.

E) **Systemic Antimicrobials**;

- **Systemic antibiotics** are appropriate and can be ***recommended*** for use in **patients** with clinical ***evidence*** of **bacterial infections**.
- **Systemic antiviral agents** should be used for the treatment of **eczema herpeticum**.

F) **Systemic Antihistamines**;

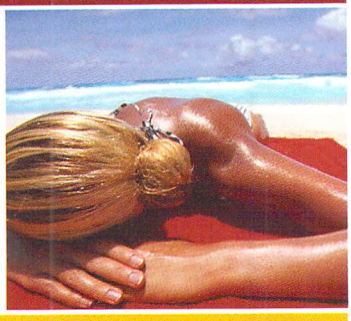
- ***Short-term***, **intermittent use** of **sedating antihistamines** may be ***beneficial*** in the setting of **sleep** ***loss secondary to*** **itch**.
- **Non-sedating antihistamines** are ***not recommended***.

Sunburn

Sunburn

- **Sunburn** is an ***acute***, ***delayed***, and ***transient*** **inflammatory response** of **normal skin** *after* ***overexposure*** to **ultraviolet (UV) radiation**, *from* **sunlight** or **artificial *sources***.
- **Sunburn** is ***characterized by*** **erythema**; ***if severe***, by **vesicles** and **bullae**, **edema**, **tenderness** and **pain**.
- An ***excess*** of **UV radiation** can be ***life-threatening*** in **extreme cases**.
- ***Excessive*** **UV radiation** (direct DNA damage) ***increases*** the **risk** of **skin cancer**.

Suntan

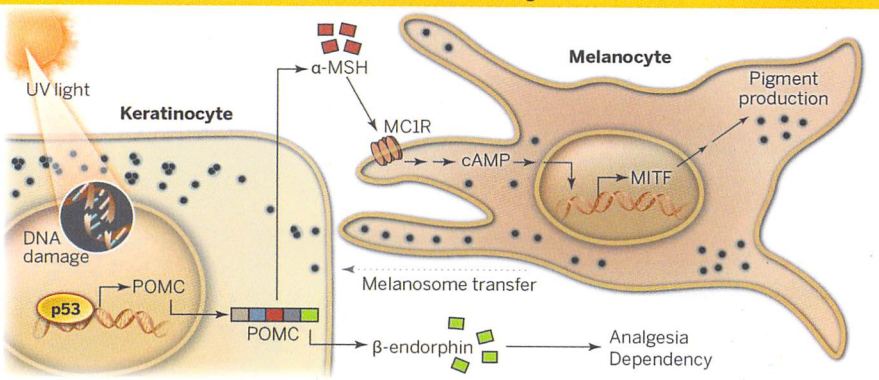


- **Sun tanning** or *simply* **tanning** is the ***process*** *whereby* **skin color** is **darkened** or **tanned**.
- The **process** is *most often* a *result of* **exposure** *to* **ultraviolet (UV) radiation** *from* the **sun** or *from* **artificial sources**, such as a **tanning bed**.
- ***Moderate*** **exposure** to the **sun** ***contributes*** to the ***production*** of **melanin**.
- ***Some*** **people** use **sunless tanning** a **chemical agents** which can *produce* a **tanning** ***without*** **exposure** to **UV radiation**, such as **Dihydroxyacetone (DHA)**.

Signs and Symptoms

- The ***first*** **signs** of a **sunburn** may ***not appear*** *for* a ***few*** **hours**;
  - ***Typical*** **Symptoms**;
    - **Redness (erythema)**, *followed by* ***varying degrees*** of **pain**;
      - **Severity** *depending on* both **duration** and ***intensity*** of **exposure**.
      - **Duration**; - Skin may turn **red** in as little as **30 minutes** but *most often* takes **2** to **6 hours**.
      - **Pain** is *usually* ***most extreme*** **6** to **48 hours** ***after*** **exposure**.
      - The **burn** ***continues*** to ***develop*** for **1** to **3 days**.
  - ***Other*** **Symptoms**;
    - **Blistering**, **swelling (edema)**, **pruritus (itching)** and **peeling skin**;
      - **Blistering** is a ***sign*** of **second degree sunburn**.
      - **Peeling skin** in **3** to **8 days**.
      - Some peeling and itching may continue for several weeks.
    - **Rash**, **nausea**, **fever**, **chills** and **fainting (syncope)**.
- **Ultraviolet radiation** ***increases*** the **risk** of **three types** of **skin cancer**: **melanoma**, **basal-cell carcinoma** and **squamous-cell carcinoma**.
- **Extreme sunburns** can be **painful** to the **point** of ***debilitation*** and may ***require*** **hospital care**.

Skin Color Changes



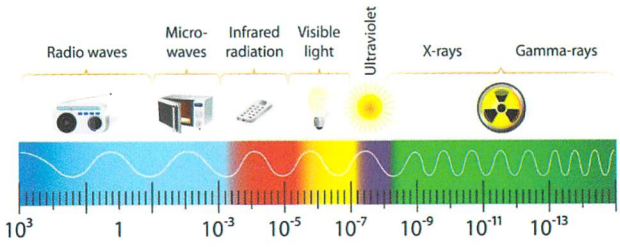
- ***When*** the **skin** is ***exposed*** to the **sun**, this can cause ***some*** **damage** in the **upper layers** of **skin** → ***activates*** **DNA damage** ***repair*** → ***induces*** **signalling** ***towards*** the **melanocytes** (which ***produce*** the **melanin pigment**).
- **Signalling** means the excretion of signalling molecules (**alpha-Melanocyte stimulating hormone**, **α-MSH**) which ***binds*** to the **MC1R receptor** (**Melanocortin 1 Receptor**) on the ***surface*** of the **melanocyte** (the cell which produces the pigment) → ***induces*** the ***production*** of **melanin**.
- The **melanin** is then ***transferred*** in the **melanosomes** to the ***adjacent*** **keratinocytes**, which are then ***better protected*** from the **sun**.
- **Melanocytes** ***produce*** **two types** of **melanin**;
  - **Eumelanin**; is found in **hair**, **areola**, and **skin**, and the **hair colors gray**, **black**, **blond**, and **brown**, it is ***more abundant*** in **people** with **dark skin**.
  - **Pheomelanin**; a **pink** to **red** hue is **found** in *particularly* ***large*** **quantities** in **red hair**, the **lips**, **nipples**, ***glans*** of the **penis**, and **vagina**.
- **Short term sun exposure** (fast reaction); are based on the ***changed*** **distribution** of **melanosomes** (granules containing melanin) from the **melanocytes** to **keratinocytes**.
- **Longer term sun exposure;** are caused by ***increased*** **pigmentation** in the **skin** as a **reaction** to the **UV exposure** by the **accumulation** of **melanin**.
- When the **body** is ***producing*** **fewer** ***new*** **melanosomes** *than are* **degraded**, **skin** ***will get*** **lighter again**.
- **Differences** in **skin color** are also *attributed to* **differences in size** and **distribution** of **melanosomes** in the **skin**, *because* of their **genetic factors**.

Human Skin Color

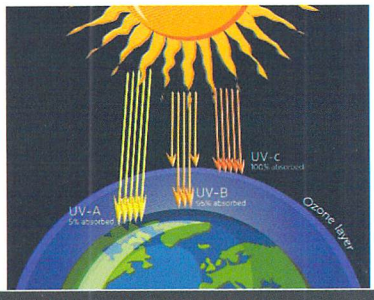
- The **Fitzpatrick scale** is a ***numerical*** **classification schema** for **human skin color**.
- It was ***developed*** in **1975** by Thomas B. Fitzpatrick as a way to estimate the response of different types of skin to ultraviolet (UV) light.
- **Von Luschan's chromatic scale** is another method of classifying skin color consist of 36 categories.
- The ***following*** list **shows 6 categories** of **Fitzpatrick scale** in ***relation to*** the **36 categories** of the older von **Luschan scale**:
  - **Type I** (scores 0–6); ***always*** **burns**, ***never*** **tans** (palest; freckles).
  - **Type II** (scores 7–13); ***usually*** **burns**, **tans** ***minimally***.
  - **Type III** (scores 14–20); ***sometimes mild*** **burn**, **tans** ***uniformly***.
  - **Type IV** (scores 21–27); **burns** ***minimally***, ***always*** **tans well** (moderate brown).
  - **Type V** (scores 28–34); ***very rarely*** **burns**, **tans** ***very easily*** (dark brown).
  - **Type VI** (scores 35–36); ***never*** **burns** (deeply pigmented dark brown to darkest brown).

Causes, Risk Factors and Complications

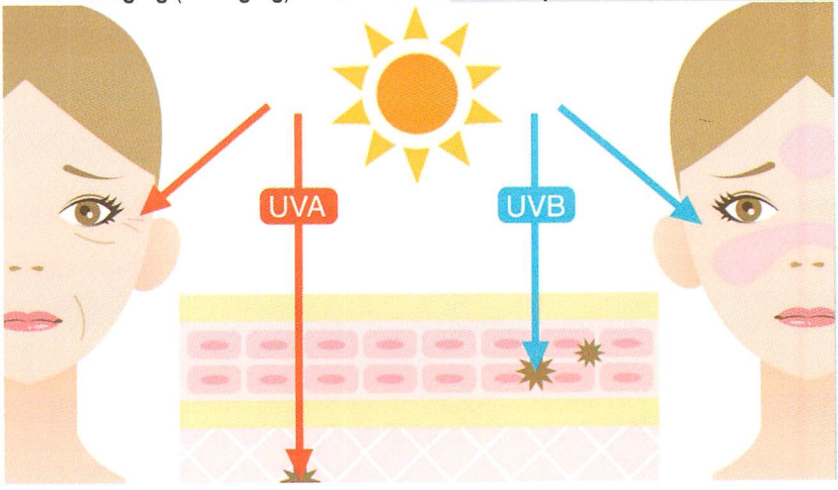
- **Causes**; ***Overexposure*** to **ultraviolet** (**UV**) **radiation**;
  - **UV** is **electromagnetic radiation** with a ***wavelength*** *from* **10 nm** to **400 nm**, ***shorter than*** that of **visible light** but ***longer than*** **X-rays**.



The Electromagnetic Spectrum



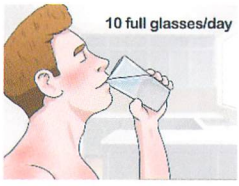
Ultraviolet A (UVA)	Ultraviolet B (UVB)
- **Wavelength** ***range*** **320** to **400 nm**. - ***Only*** **5%** is **blocked** by the **Ozone layer**. - ***More*** **uniformly** ***throughout*** the **day**. - ***Deep*** **skin penetration** and ***absorbed*** *by* **epidermis** and **dermis** and *can cause* **cellular** ***damage***. - ***Causes*** **skin Aging** (**A** = **Aging**).	- **Wavelength** ***range*** **280** to **320 nm**. - **95%** is **blocked** by the **Ozone layer**. - ***Not*** **uniformly** ***throughout*** the **day**. - ***Poor*** **skin penetration** and ***absorbed*** by **epidermis** ***only***. - ***Causes*** **skin Burns** (**B** = **Burns**). - It is ***required for*** **Vitamin D** ***activation***.



- **Risk Factors**;
  - **Peoples** *with* **light skin**, **blue eyes**, and **red** or **blond hair**.
  - **Living** or **vacationing** *somewhere* **sunny**, **warm** or at high **altitude**.
  - ***Working*** **outdoors**.
  - ***History*** of **sunburn**.
  - ***Regularly*** **exposing** ***unprotected*** **skin** to **UV light**.
  - ***Taking*** **photosensitizing medications** such as; ***certain*** **antibiotics** (**Tetracyclines**, **Fluoroquinolones** and **Sulfonamides**), ***certain*** **antifungals**, **NSAIDs**, **diuretics**, **retinoid**, **sulfonylureas**, **statins** and **neuroleptic drugs**.
- **Complications**;
  - **Premature skin aging**; **wrinkles**, **dry**, **rough skin**, **freckles** and **dark** or **discolored spots**.
  - **Skin cancer** and **eye damage**.

Managements (AAD recommendations)

1) ***Frequent* cool baths** or **showers** (to help relieve the pain);
   - Then, apply a moisturizer to help trap the water in the skin.
2) **Topical moisturizer**;
   - Use a moisturizer that contains aloe vera or soy (to help soothe sunburned skin).
3) **Pain relieve medications**;
   - Consider taking NSAIDs such as ibuprofen to help reduce any swelling, redness and discomfort.
4) **Topical Corticosteroids**;
   - Apply a Hydrocortisone cream to help reduce inflammation and discomfort.
   - Do not treat sunburn with local anaesthetic such as benzocaine, as these may irritate the skin or cause an allergic reaction.
5) ***Drink* extra water**;
   - A sunburn draws fluid to the skin's surface and away from the rest of the body.
   - Drinking extra water when to prevent dehydration.



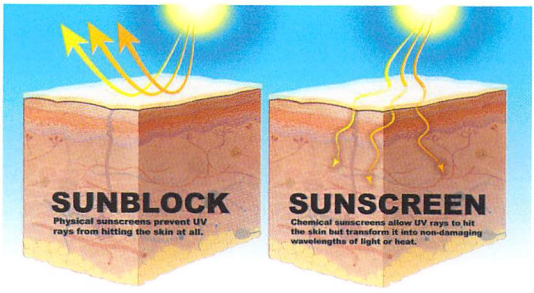
* ***Other* recommendations**;
   - If skin **blisters** is ***present***, ***allow*** the **blisters** to **heal** (not pop it).
   - **Take *extra* care** to ***protect* sunburned skin** while it **heals** (avoid exposure to sun during healing).
   - **Wear clothing** that ***covers*** the **skin *when* outdoors**.
      - Tightly-woven fabrics work best.
      - When hold the fabric up to a bright light, shouldn't see any light coming through.

Prevention

1) ***Avoid* sun exposure** *between* **10 am** and **4 pm**.
2) ***Avoid* sun tanning** and **tanning beds**.
3) ***Use* sunscreen *frequently*** (SPF of 30 or greater & broad-spectrum protection against UVA & UVB rays)
4) ***Wear* sunglasses** (with UVA and UVB protection) ***when* outdoors**.
5) ***Be aware* of photosensitizing medications**.

Sunscreen

- **Sunscreen** (also known as sunblock, sun cream or suntan lotion); is a **lotion**, **spray**, **gel** or ***other* topical product** that ***absorbs*** or ***reflects*** ***some*** of the **sun's ultraviolet** (**UV**) **radiation** and thus ***helps* protect *against* sunburn**.
   - N.B.;
      - **Sunblock** (**Physical Sunscreen**) *typically refers to* **opaque sunscreen** that is ***effective*** at ***blocking both* UVA** and **UVB rays** and uses a ***heavy* carrier oil** to ***resist*** being **washed off**.
      - **Titanium Dioxide** and **Zinc Oxide** are two of the ***important*** **ingredients** in **sunblock**.
      - **Sunscreen** (**Chemical Sunscreen**) is ***more* popular *than* Sunblock** (due to sunblock has greasy appearance).



Physical Sunscreen (Sunblock)

- It act as **physical barrier** to ***reflect*** and ***scatter*** *about* **99%** of **light**, but ***less*** **cosmetically *accepted*** than **chemical sunscreen *because*** it has **greasy appearance**.
- There is ***no*** **chemical reaction** and ***no*** **free radicals** are ***produced***.
- **Examples**; **Titanium dioxide**, **Red Petrolatum** and **Zinc Oxide**.

Chemical Sunscreen (Sunscreen)

- ***Protect*** the **skin** by ***absorbing*** the **light particles**.
- *When* this **energy** is **absorbed**, the **molecules** of the **sunscreen** are **chemically *react*** and ***destroyed*** **it**.
- This **chemical reaction *generates*** **free radicals**, ***secondary*** **free radicals** may ***accelerate*** **skin aging *process*** *after* **long period** of **application** → ***potential*** of **secondary damage**.
- **Sunscreen *contains*** **exceptionally powerful antioxidants** to ***reduce*** **free radical *activities*** and the ***potential*** of **secondary damage**. These **antioxidants** such as **grape extract**, **vitamin E**, **green tea**, etc.
- ***Examples***: - **PABA** (**Para-amino-benzoic acid**) (**Padimate-O** and **Glyceryl PABA**).
  - **Cinnamates** (**Cinoxate** and **Octocrylene**).
  - **Salicylates** (**Ethyl salicylate** and **Homosalicylate**).
  - **Benzophenones** (**Oxybenzone** and **Dioxybenzone**).
  - **Miscellaneous** (**Avobenzone** and **Sulisobenzone**).
- **Sunscreen** *usually* **applied 20-30 minutes** *before* ***going*** **outdoors** and ***reapply*** ***every*** **2 hours**, ***after*** **heavy sweating** or ***after*** **being** in **water**.

Measurements of Protection

A) Sun Protection Factor (SPF); The **SPF** of a **sunscreen** is a **laboratory measure** of the ***effectiveness*** of **sunscreen**; the ***higher*** the **SPF**, the ***more*** **protection** a **sunscreen offers *against*** **UVB**.

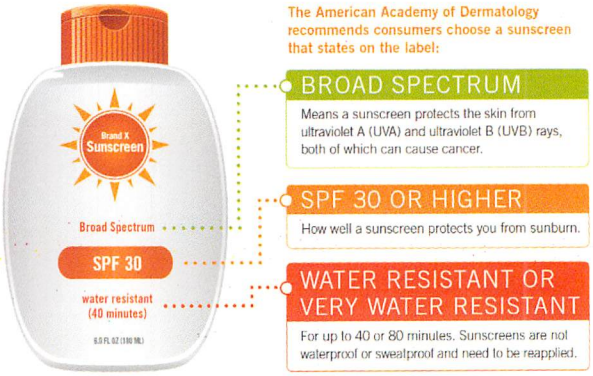
- **SPF** = $\frac{\text{The amount of light that induces redness in sunscreen-protected skin}}{\text{The amount of light that induces redness in unprotected skin}}$
- **The SPF Scale** (not linear);
  - **SPF 15** ⇨ ***Protect*** **93%** of **UVB *rays***.
  - **SPF 30** ⇨ ***Protect*** **97%** of **UVB *rays***.
  - **SPF 50** ⇨ ***Protect*** **98%** of **UVB *rays***.
  - **SPF 100** ⇨ ***Protect*** **99%** of **UVB *rays***.
- So, one way of looking at this is that SPF 30 only gives you 4% more protection than SPF 15.
- Sunscreens with really high SPFs, such as SPF 100, do not offer significantly greater protection than SPF 30 and mislead people into thinking they have more protection than they actually do.

B) Sunscreen spectrum; **broad-spectrum sunscreens** are *designed to* ***protect*** **against *both*** **UVB** & **UVA**

C) Substantively: ***Ability*** of the **sunscreen** to ***adhere*** to the **skin** *while* **swimming** or **perspiring**.

D) Water Resistance: ***Indicate*** that the **formula *retain*** **SPF** ***after*** **40 min** of ***activity*** in **water**, **sweating** and **perspiring**.

E) Very Water Resistance: ***Indicate*** that the **formula *retain*** **SPF** ***after*** **80 min** of ***activity*** in **water**, **sweating** and **perspiring**.



Skin Aging and Wrinkles

- **Skin aging** is ***influenced by*** **many factors** *including* **ultraviolet radiation**, ***excess*** **alcohol consumption**, **tobacco abuse** and **environmental pollution**.
- ***Within*** the **skin**, **aging** is ***associated with*** a ***loss*** of **fibrous tissue**, ***slower*** **rate** of **cellular renewal**, and a ***reduced*** **vascular** and **glandular network**.
- **Barrier function** that ***maintains*** **cellular hydration** also *becomes* ***impaired***.
- The **subcutaneous tissue** ***flattens***, *particularly* in the **face**, **hands** and **feet**.

Combating Skin Aging

A) Dietary Strategies *to* **Promote Youthful Skin Appearance**;

- **Glycemic Control**; High glycemic diet may contribute to inflammatory skin conditions such as acne, rosacea, psoriasis, and eczema.
- **Essential Fatty Acids Intake**; Fish oil rich in the omega-3 oils eicosapentaenoic and docosahexaenoic acids (EPA and DHA) inhibit the production of inflammatory metabolites.
- **Antioxidants**; Antioxidants are chemicals that are able to donate an electron to a free radical, stabilizing the free radical and stopping the chain of chemical reactions and potential damage.

B) Topical Care: - **Sunscreen** (with dual protection against UVA and UVB).
- **Light daily moisturizer** and **Intensive nighttime moisturizer**.

* **Supplemental Nutrients** to **Support Skin Health**;

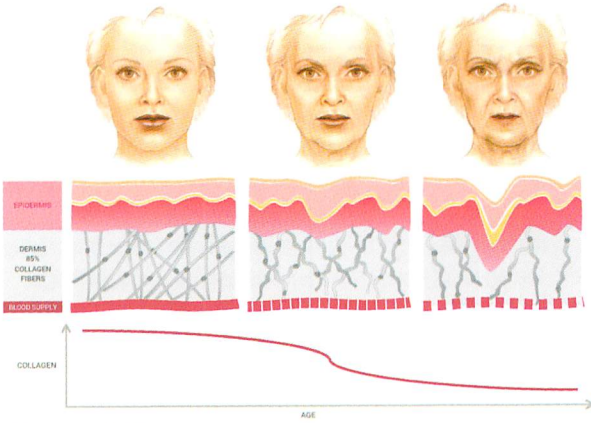
Curcumin	400-800 mg daily
Trans-Resveratrol	250-500 mg daily
Coenzyme Q10 (CoQ10)	100-200 mg daily
Selenium	200-400 mcg daily
Vitamin E	350 mg daily
Vitamin A	5000 IU daily
Fish oil	1400 mg EPA & 1000 mg DHA daily
Lycopene	15 mg daily
Vitamin D	5000-8000 IU daily
Green tea, standardized extract	725-1450 mg daily
Grape extract	150 mg daily
Blend of dark berry extracts	700-1400 mg daily
Fern extract	240-480 mg daily
Soy isoflavone blend	135-270 mg daily

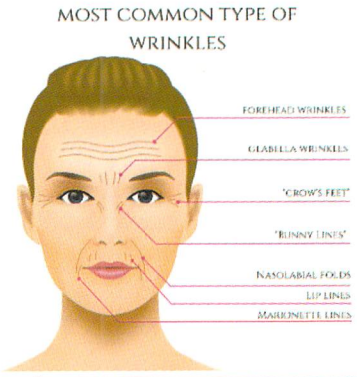
Wrinkles

- **Wrinkles** are **lines**, **furrows** or **creases** ***occurring*** on the **skin surface**, *due to* ***underlying*** **alterations** in the **dermal collagen** and **elastic fibers**.
- **Wrinkles** are a ***natural*** **part** of **aging**, but they're ***most prominent*** on **sun-exposed skin**, such as the **face**, **neck**, **hands** and **forearms**.
- *Although* **genetics** are the ***most*** **important** ***determinant*** of **skin structure** and **texture**, **sun exposure** is ***major*** **contributor** to **wrinkles**.

- **Causes** (**Etiology**);
  - **Aging** (intrinsic and extrinsic).
  - **Premature aging syndrome** (such as Progeria) and **cutis laxa**.
  - **Exposure** to **ultraviolet** (**UV**) **light**.
  - **Smoking** and **poor nutrition**.
  - ***Repeated*** **facial expressions**.
  - **Gender** (Women develop more wrinkles around mouths than men).

- Types;
  - *According* to **depth**;
    - **Fine wrinkles**; < 1mm in depth according to periorbital areas (crow's feet), cheeks and lips.
    - **Medium-depth wrinkles**; Represent an exaggeration of the normal skin markings taking the form of lines intersecting each other (polygons).
    - **Deep wrinkles**; >1 mm in depth according to the animation parts.
  - *According* to **location**;
    - **Nasolabial furrows** (smile lines).
    - **Perioral wrinkles** (around the mouth and lips).
    - **Vertical-lateral forehead wrinkles**.





- **Sleep wrinkles**; are ***created*** and **reinforced** when the **face** is **compressed *against*** a **pillow** or **bed surface** in **side** or **stomach** sleeping ***positions*** *during* **sleep**.
- **Water-immersion wrinkling**; This is a ***temporary*** **skin condition** where the **skin** on the **palms** of the **hand** or **feet *becomes*** **wrinkly**;
  - The common explanation was based on water absorption in the keratin-laden epithelial skin when immersed in water, causing the skin to expand and resulting in a larger surface area, forcing it to wrinkle.

Water-immersion Wrinkling

Managements

A) **Combating skin aging**; *see previous topic*

B) **Anti-aging cosmetics**; **Anti-aging cosmetic preparations *include*** *conventional* **moisturising** with a **specific anti-aging ingredients**, such as;

- **Retinol** (*in the form of* **Retinyl Palmitate**); reduce fine lines and pores.
- **Epidermal growth factor**; stimulate cell renewal and collagen production.
- **Hyaluronic acid**; promotes collagen synthesis, repair and hydration.
- **Alpha hydroxy acid** (**AHA**) and **beta hydroxy acid** or ***other*** **chemical peels**; enhances the exfoliation of the epidermis and the exposes new skin cells and can help improve appearance.
- **Peptides**, such as **Matryxil** and **Copper Peptides**; boosting production of collagen and elastin.
- **Coenzyme Q10**; regulate energy production in cells.
- **Argireline** (**acetyl hexapeptide-3**); relaxes facial muscles to prevent wrinkles formation.
- **Anti-oxidants**; protect cells from the damage.
- **Broad-spectrum sunscreens**; provide a high level of UVA protection.
- **Vitamin C**; antioxidants and it is also thought to help the healing process.

C) Chemical peeling; by ***using*** **one** or **more chemical exfoliating agents** to the **skin**, ***resulting*** in ***destruction*** of **portions** of the **epidermis** and/or **dermis** with ***regeneration*** of ***new*** **epidermal** and **dermal tissues**.

- **Chemical peeling agents**, such as; **Trichloroacetic acid** (**TCA**), **Salicylic acid**, **Alpha hydroxy acid** (**AHA**) and **Phenol**.

D) Mechanical peeling; ***non-chemical*** **skin exfoliation**;

- **Dermabrasion**;
  - This procedure consists of sanding down (planing) the surface layer of skin with a rapidly rotating brush.
  - The planing removes the skin surface, and a new layer of skin grows in its place.
  - Used to remove scars, stretch marks, wrinkles, pigmentation, and age spots.
- **Microdermabrasion**:
  - This technique is similar to dermabrasion, but less surface skin is removed.
  - It's done using a vacuum suction over face, while aluminum oxide crystals essentially sandblast skin.

E) Augmentation therapy by filler injection; by ***injection*** of **soft tissue filler** into the **skin** to help ***fill*** in **facial wrinkles**, ***restoring*** a **smoother appearance**.

- **Fillers**, such as **Hyaluronic acid**, **Collagen**, **Calcium hydroxylapatite**, **Polycaprolactone**, **Polymethylmethacrylate** and **Polylactic acid**.

F) Botulinum toxin injection;

Botulinum Toxin Type A (**Botox®**)

- When injected in ***small*** **doses** into ***specific*** **muscles**, **Botox®** ***blocks*** the **chemical signals** that cause **muscles** to ***contract*** (**Acetylcholine**).
- When the **muscles relax**, the **skin flattens** and ***appears*** **smoother** and ***less*** **wrinkled**.
- **Botox®** works well on **frown lines** between the eyebrows and across the forehead, and **crow's-feet** at the corners of the eyes.
- **Results** *typically* ***last*** about **3** to **4 months**.
- ***Repeat*** **injections** are *needed to* ***maintain*** **results**.

G) Skin Tightening by laser or energy based devices;

- ***Remove*** **thin layers** of **skin** and ***stimulates*** **collagen** ***production***.

H) Skin Lifting by threads or surgical operations (Facelift Surgery);

- The **face-lift procedure** *involves* ***removing*** **excess skin** and **fat** in the ***lower*** **face** and **neck** and ***tightening*** the **underlying muscle** and **connective tissue**.

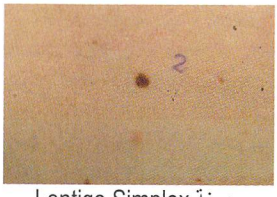
Hyperpigmentation

- **Hyperpigmentation** is the ***darkening*** of an **area** of **skin** *caused by* ***increased*** **melanin**.
- **Hyperpigmentation** can be ***caused by*** **sun damage**, **inflammation**, or other **skin injuries**, including those *related to* **acne vulgaris**.
- The ***most common*** **forms of hyperpigmentation**;

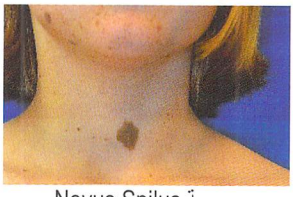
1) **Melasma**;
   - **Melasma** [muh-LAZ-muh] is a ***common***, *characterized by* a *slowly* **progressive**, with an ***irregular*** **coloration**, *ranging from* **light brown** to **gray** and **dark brown**.
   - **Melasma** *appears* on **women's skin** ***much more*** often ***than*** **men's skin**.
   - **Causes** is ***not*** *yet* **clear**.
   - ***Common*** **triggers**;
     * **Sun Exposure**.
     * **Hormonal Changes**.
     * **Genetic Predisposition**.
     * **Skin Care Products**.

Melasma كلف

2) **Lentigines**;
   - The term **lentigo** ***encompasses*** an *array of* ***related*** **hyperpigmented lesions**, which include **lentigo simplex**, **nevus spilus**, **agminated lentigines**, **solar lentigo**, and **lentigo maligna**.

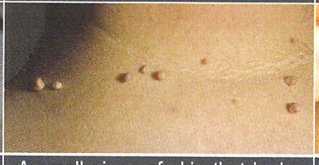
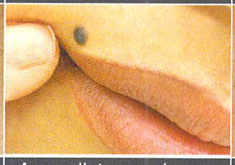


Lentigo Simplex حسنة



Nevus Spilus وحمة

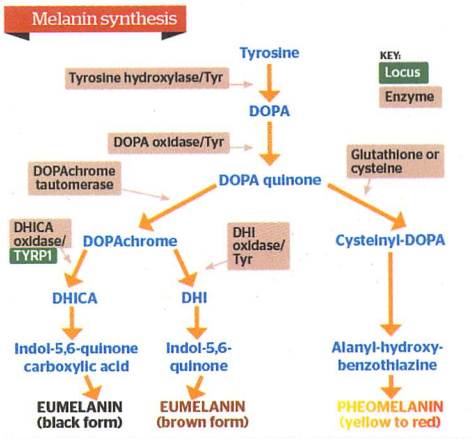
   - They are ***resulting from*** an ***increased*** **number** of **melanocytes** in the **epidermis**.
   - **Lentigines** by ***themselves*** are **benign**.
   - ***Differential Diagnosis***;

Freckle	Skin Tag	Mole	Melanoma
			
A small brown spot, more common in people with red or light-colored hair and people with lighter skin and can be caused by exposure to the sun (↑ amount of melanin).	A small piece of skin that looks like it's hanging off the skin, not painful and not dangerous. More common in middle-aged, obese adults. Treatments include freezing, or cutting off.	A small tan or brown spots on the skin, may be flat or raised. Most moles are genetically predetermined before we are born.	Irregular moles may develop into skin cancer called melanoma. Cancer of melanocytes.

3) **Post-inflammatory Hyperpigmentation** (**PIH**);
   - **PIH** is ***temporary*** **pigmentation** that *follows* **injury** (e.g. thermal burn) or **inflammatory disorder** of the **skin** (e.g. **dermatitis**, **infection**).
   - ***More severe*** **injury** *results* in **postinflammatory hypopigmentation**, which is *usually* **permanent**.
   - The **hyperpigmentation spots** ***range from*** **light brown** to **black** in **color**. The **patches** may ***become*** darker if ***exposed to*** **sunlight** (**UV rays**).

Managements

* **Avoidance** of **sunlight** is ***required***, and use of ***broad-spectrum*** **sunscreens** in **outdoors**.
* **Topical Managements**;
  - **Hydroquinone** (**HQ**); (2% [OTC] or 4% [prescription]) inhibits tyrosinase, an enzyme involved in the production of melanin.
  - **Tretinoin** (0.1%); increases keratinocytes turnover.
  - **Azelaic acid** (20%); thought to decrease the activity of melanocytes.
  - **Cysteamine hydrochloride** (5%); inhibition of melanin synthesis pathway.
  - **Corticosteroids** (**Dexamethasone**, **Fluocinolone acetonide**).
  - **Others**; **Kojic acid**, **Arbutin**, **Licorice extracts**, **Mequinol**, **Niacinamide**, **N-acetyl glucosamine** and **soy**.



Melasma Triple Therapy

* **Tri-Luma®**; **Hydroquinone** 4% + **Tretinoin** 0.05% + **Fluocinolone acetonide** 0.01%
* **Pigmanorm®**; **Hydroquinone** 4% + **Tretinoin** 0.1% + **Hydrocortisone** 1%

for the short-term (up to 8 weeks) treatment of moderate to severe melasma

- ***Oral*** **Tranexamic acid** has *shown* to *provide* ***rapid*** and *sustained* **lightening** in **melasma** by ***decreasing*** **melanogenesis** in ***epidermal*** **melanocytes**.

- **Procedures**;
  - **Chemical peeling**; **Trichloroacetic acid** (**TCA**), **Salicylic acid**, **Alpha hydroxy acid** (**AHA**) and **Phenol**.
  - **Mechanical peeling**;
    - **Microdermabrasion**.
    - **Dermabrasion**.
  - **Laser treatment**;
    - **Pulsed CO_2 laser**.
    - **Q-switched alexandrite laser**.

Psoriasis

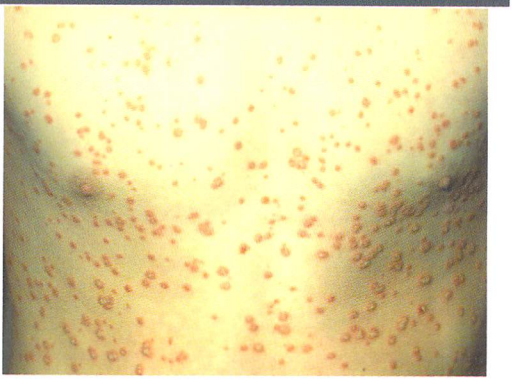
- **Psoriasis** [so-ri-a-sis] is an **autoimmune disease** that ***affects*** the **life cycle** of **skin cells** (speeds up the life cycle of skin cells).
- **Psoriasis** is a ***chronic*** **inflammatory skin disease** that causes **cells** to ***build up*** **rapidly** on the **surface** of the **skin** ***forming*** **thick silvery scales** and **itchy**, **dry**, **red patches** that are *sometimes* **painful**.
- There are **5 main types** of **psoriasis**: **Plaque**, **Guttate**, **Inverse**, **Pustular** and **Erythrodermic**.
- **Plaque psoriasis** (**psoriasis vulgaris**) ***makes up*** *about* **90%** of **cases**.
- **Causes**; The **cause** of psoriasis is **not fully understood**, but a number of theories exist.
- **Symptoms**;
  - **Psoriasis signs** and **symptoms** can ***vary*** *from* **person** *to* **person** but *may include* **one** or **more** of the ***following***;
    - **Red patches** of **skin** ***covered with*** **silvery scales**.
    - **Small scaling spots**.
    - **Dry**, **cracked skin** that ***may*** **bleed**.
    - **Itching**, **burning** or **soreness**.
    - **Thickened**, **pitted** or **ridged nails**.
    - **Swollen** and **stiff joints**.

Types of Psoriasis

Plaque Psoriasis

- The most common form.
- Dry, raised, red skin lesions (plaques) covered with silvery scales.

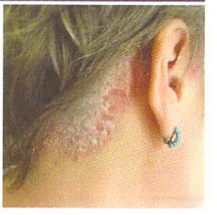
Guttate Psoriasis



- It's marked by small, water-drop-shaped sores on the trunk, arms, legs and scalp.
- The sores are covered by a fine scale and aren't as thick as typical plaques.

Scalp Psoriasis

- Red, itchy areas with silvery-white scales.
- Flakes of dead skin in the hair or on the shoulders, especially after scratching the scalp.



Nail Psoriasis

- Abnormal nail growth and discoloration.
- Loose and separate from nail bed (onycholysis).
- Severe cases may cause the nail to crumble.

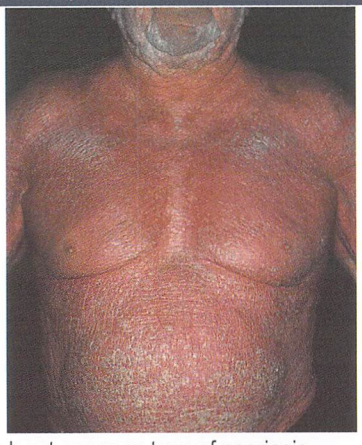
Inverse Psoriasis

- Mainly affecting the skin in the armpits, in the groin, under the breasts and around the genitals.
- Inverse psoriasis causes smooth patches of red, inflamed skin.

Pustular Psoriasis

- This uncommon form of psoriasis can occur in widespread patches.
- It generally develops quickly, with pus-filled blisters appearing just hours after the skin becomes red and tender.
- The blisters dry within a day or two, but may reappear every few days or weeks.

Erythrodermic Psoriasis



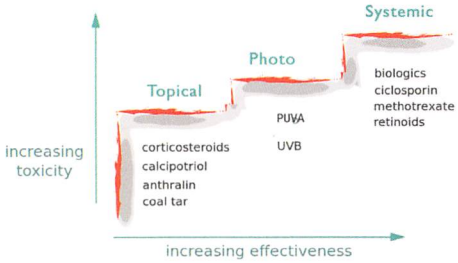
- The least common type of psoriasis.
- Erythrodermic psoriasis can cover the body with a red, peeling rash that can itch or burn intensely.
- It may be triggered by severe sunburn, by corticosteroids and other medications.

Psoriatic Arthritis

- In addition to inflamed, scaly skin, psoriatic arthritis causes pitted, discolored nails and the swollen, painful joints that are typical of arthritis.
- It can also lead to inflammatory eye conditions, such as conjunctivitis.
- Symptoms range from mild to severe and psoriatic arthritis can affect any joint.
- Although the disease usually isn't as crippling as other forms of arthritis, it can cause stiffness and progressive joint damage that in the most serious cases may lead to permanent deformity.

Managements [American Academy of Dermatology (AAD) Guidelines]

- There is ***no* cure** *available* for **psoriasis**, the **goal** is to **find** the ***most effective* way** to ***slow* cell turnover** with the ***fewest* possible side effects**.
- *Many* **treatment options** exist;
  - **Topical agents** for **mild disease**.
  - **Phototherapy** for **moderate disease**.
  - **Systemic agents** for **severe disease**.



A) Topical Treatments

1) Topical Corticosteroids

- **Topical corticosteroids** are ***powerful*** **anti-inflammatory drugs**, they are the ***most frequently*** **prescribed medications** for **treating** ***mild*** to ***moderate*** **psoriasis**.
- **Local Toxicities**; **skin atrophy**, **telangiectasia**, **striae**, **purpura**, **contact dermatitis** and **rosacea**.

2) Vitamin D Analogues

Calcipotriene or Calcipotriol (Dovonex®)	**Calcitriol** (Vectical®)

- **Calcipotriene** or **Calcipotriol** is a ***synthetic*** **derivative** of **Calcitriol** (*form of* vitamin D).
- **Calcitriol** is the ***active*** **metabolite** of **vitamin D**.
- **Mechanism of action**; the mechanism of vitamin D analogues in psoriasis is believed to be mediated by their ***binding*** to **vitamin D receptors**, which ***leads to*** *both* the ***inhibition*** of **keratinocyte** ***proliferation*** and ***enhancement*** of **keratinocyte** ***differentiation***.
- **Local side effects**; such as **burning**, **pruritus**, **edema**, **peeling**, **dryness**, and **erythema**.
- **Calcipotriene** is ***inactivated*** by **UVA**, it is **important** to ***apply*** **Calcipotriene** ***after*** and ***not before*** **UVA exposure**.
- **Calcitriol** (**Vectical®**) is ***expensive***, but may be ***equally*** **effective** and *possibly* ***less*** **irritating**.
- **Vitamin D Analogues** in ***combination with*** **topical corticosteroids** (**Calcipotriene** + **Betamethasone**; **Taclonex®**) ***gives*** **added benefit**.
- **Pregnancy**; **Category C**.

3) Tazarotene

Tazarotene (Tazorac®)

- **Oral retinoids** have been **used** in the ***treatment*** of **psoriasis** for ***many*** **years**, the **topical retinoid Tazarotene** ***first*** became available for the **treatment** of **psoriasis** in **1997**.
- **Mechanism of action**; **Tazarotene** is thought to function by ***normalizing*** **abnormal keratinocyte** ***differentiation***, ***diminishing*** **hyperproliferation**, and by ***decreasing*** **expression** of **inflammatory markers**.
- **Most common side effect**; **local irritation**; Irritation may be reduced by;
  - Use of the cream formulation.
  - Use of the lower concentration product.
  - Combination use with moisturizers or in combination with topical corticosteroids.
- **Pregnancy**; **Category X**.

4) Topical Calcineurin Inhibitors

Tacrolimus (Protopic®)	**Pimecrolimus** (Elidel®)

- **Calcineurin inhibitors** ***function*** by ***blocking*** the **synthesis** of **numerous inflammatory cytokines** that **play** an ***important*** **role** in the **pathogenesis** of **psoriasis**.
- **Most common side effect**; **burning** and **itching**, that generally ***reduces*** with **ongoing usage**.
- **Black box warning**; ***potential*** **risk** for the ***development*** of **malignancies**.
- **Pregnancy**; **Category C**.

5) Other Topical Treatments

A) Non-medicated Topical Moisturizers; **Moisturizing** *don't* ***heal*** **psoriasis**, but they can ***reduce*** **itching** and **scaling**.

B) Salicylic Acid; **Salicylic acid** is a **topical keratolytic agent**, it is often ***combined with*** other **topical therapies**, *including* **corticosteroids** and ***topical*** **immunomodulators**.

C) Anthralin (Psoriatec®);

- **Anthralin** can **irritate skin**, and it **stains** (yellowy-brown) **virtually *anything*** it **touches**, including skin, clothing, countertops and bedding.

D) Coal Tar (Polytar®);

- **Coal tar**, a **distillation product** from **coal**, is a ***mixture*** of **thousands** of **compounds**.
- **Coal tar** has been ***used*** in the **treatment** of **psoriasis** for ***more than*** **100 years**.

E) Combinations of Topical Therapies;

- **Corticosteroids** and **Salicylic Acid**; Salicylic acid enhance the efficacy of corticosteroids by increasing penetration.
- **Corticosteroids** and **Vitamin D Analogues**; more efficacious than either therapy alone, with fewer side effects.
- **Corticosteroids** and **Tazarotene**; more effective than therapy with tazarotene alone.
- **Tacrolimus** and **Salicylic Acid**; Salicylic acid enhance the efficacy of tacrolimus.

B) Phototherapy and Photochemotherapy

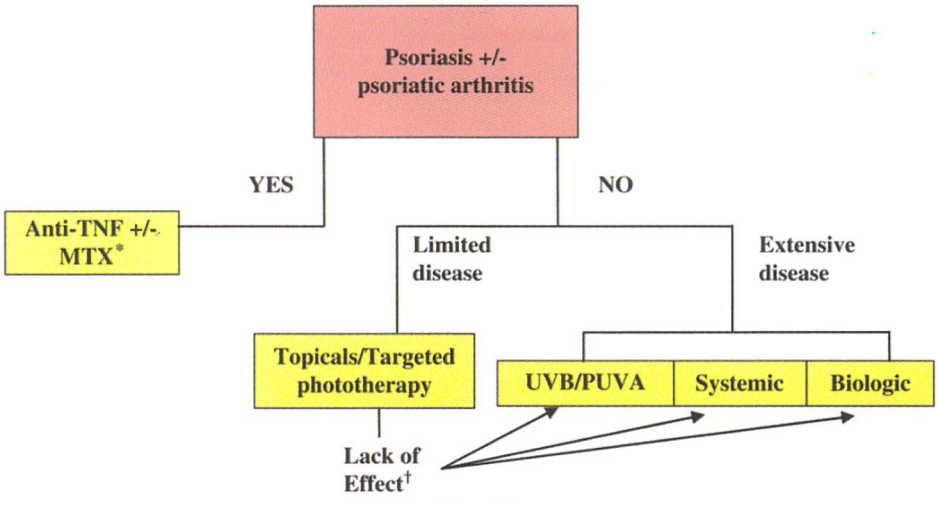
- **Various spectra** of **UVB** and **UVA wavelengths *alone*** or in ***combination*** with **medications** have been used to treat **psoriasis**.
- *Because* **keratinocyte hyperproliferation** is a ***hallmark*** **feature** of **psoriasis**, it was originally believed that the ***mechanism*** of ***action*** of **UV light *treatment*** in **psoriasis** was *through* a ***direct effect*** of **UV light** on **DNA** by ***inhibition*** of **cellular turnover**.
- **UVB** and **psoralen *plus*** **UVA** (**PUVA**) can ***induce*** **apoptosis** of **T lymphocytes**, which may ***play*** an **important role** in the ***mechanism*** involved in ***remissions*** of **psoriasis**.

C) Traditional Systemic Agents

- **Traditional systemic agents** such as; **Methotrexate**, **Cyclosporine**, **Retinoids**, **Azathioprine**, **Fumarates**, **Hydroxyurea**, **Leflunomide**, **Mycophenolate Mofetil**, **Sulfasalazine**, **Tacrolimus** and **6-thioguanine**.

D) Biologics

1) **Biologics** that ***Target*** **Pathogenic T Cells**; **Alefacept** (**Amevive®**) and **Efalizumab** (**Raptiva®**).
2) **TNF inhibitors**; **Adalimumab** (**Humira®**), **Etanercept** (**Enbrel®**) and **Infliximab** (**Remicade®**);



Decision Tree

- TNF; Tumor Necrosis Factor
- MTX; Methotrexate
- PUVA; Psoralen plus UV-A

Vitiligo

- **Vitiligo** [vit-uh-lie-go] is a ***condition*** in which the **skin** ***loses*** **melanin**, the **pigment** that ***determines*** the **color** of the **skin**, **hair** and **eyes**.
- **Vitiligo** occurs when the **cells** that ***produce*** **melanin** (**melanocytes**) ***die*** or ***no longer*** form **melanin**, causing *slowly* ***enlarging*** **white patches** of ***irregular*** **shapes** to ***appear on*** the **skin**.
- **Vitiligo** usually ***starts as*** **small areas** of **pigment** ***loss*** that ***spread*** *with* **time**.
- There is ***no cure*** for **vitiligo**.
- The **goal** of **treatment** is to ***stop*** or ***slow*** the **progression** of **pigment** ***loss***.
- Causes; It *may be* ***due to*** an **immune system disorder**.
- Types of Vitiligo (*most common*);
  - * **Generalized** (**Non-segmental** or **Bilateral**);
    - In this most common subtype, pigment loss is widespread across many parts of the body, often symmetrically.
  - * **Segmental** (**Unilateral**);
    - Loss of skin color occurs on only one side of the body.
    - This type tends to occur at a younger age, progress for a year or two, then stop.
  - * **Focal**;
    - Depigmentation is limited to one or a few areas of the body.
- Managements;
  - The goal in ***treating*** **vitiligo** is to ***restore*** **color** (**pigment**) to the **skin** and ***improve*** it is **appearance**.
  - ***Depending*** on the **type** of **therapy**, **treatment** for **vitiligo** may take *from* **six** to **18 months**.
  - **Treatment choices** are ***based on*** the ***number*** of **white patches** and how ***widespread*** they are.
  - ***Each*** **person** ***responds*** **differently** to **treatment**, and a ***particular*** **therapy** *may* **not work**.

A) Medical Therapies

1) Topical Corticosteroid Therapy.
2) Vitamin D Analogues; Calcipotriene (Dovonex®).
3) Photochemotherapy (Psoralen + Ultraviolet A = PUVA)
4) Narrow-Band Ultraviolet B (NB-UVB) Therapy;
5) Excimer Laser;
6) Depigmentation;
   - Depigmentation involves fading the rest of the skin on the body to match the already-white areas.
   - If vitiligo more than 50% of the body, depigmentation may be the best treatment option.
   - In this procedure, the drug Monobenzone (Benoquin®) is applied twice a day to the pigmented areas of the skin until they match the already-depigmented areas.

B) Surgical Therapies

1) Autologous Skin Grafts; This type of skin grafting uses own tissues (autologous).
2) Suction Blister Grafting.
3) Tattooing (Micropigmentation).
4) Melanocyte Transplant.

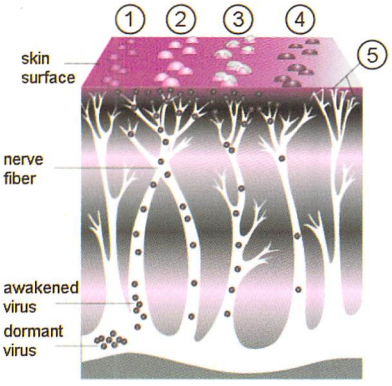
Cold Sores

- **Cold Sores** (**fever blisters** or **herpes labialis**) are **tiny**, **fluid-filled lesions** that occur on and ***around*** the **lips**.
- These **blisters** are often ***grouped*** **together** in **patches**.
- **Cold sores** ***spread*** *from* **person** to **person** by **close personal contact**, *such as* **kissing**.
- **Cold sores** *usually* **heal** *within* **2 weeks**.
- **Causes**;
  - **Cold sores** are ***caused by*** *certain* **strains** of the **Herpes Simplex Virus** (**HSV**).
    - **HSV-1**; usually causes **cold sores**.
    - **HSV-2**; usually responsible for **genital herpes**.
  - *However*, either type can cause **sores** in the **facial area** or on the **genitals**.
- **N.B.**; - ***Once*** **had** an **episode** of **herpes infection**, the **virus** ***lies*** **dormant** in **nerve cells** in the **skin** and *may* ***emerge*** **again** as an **active infection** ***at*** or ***near*** the **original site**.
  - **Recurrence** may be ***triggered by*** **fever**, **menstruation**, **stress**, **fatigue**, **exposure** to the **sun** and ***changes*** in the **immune system**.
- **Treatments**; **Cold sores** *generally* **clear up** ***without*** **treatment** ***within*** **2 weeks**.
  - **Antiviral medications** *can* ***help*** **cold sores heal** ***more quickly*** and may ***reduce*** the **frequency** of **recurrences**.
  - ***Several*** **types** of *prescription* **antiviral drugs**, *includes*;
    - **Acyclovir** (**Zovirax®**); 200 mg 5 times daily for 5-10 days OR use topical **Acyclovir** up to 5 times daily.
    - **Valacyclovir** (**Valtrex®**); 2 g orally every 12 hrs for 1 day.
    - **Penciclovir** (**Denavir®**); used only as a topical.
    - **Famciclovir** (**Famvir®**); 250 mg orally every 8 hrs for 7-10 day and in recurrence; 1500 mg orally once.
    - **Docosanol** (**Abreva®**); used only as a topical.
    - **Trifluridine** (**Viroptic®**); can used and it is available as eye drops.
- **Differential Diagnosis**;

Canker Sore	Impetigo around the mouth
- Canker sores, also called aphthous ulcers, are small, shallow lesions that develop on the soft tissues in the mouth or at the base of the gums. - Unlike cold sores, canker sores don't occur on the surface of the lips and aren't contagious. - They can be painful, however, and can make eating and talking difficult. - Most canker sores go away on their own in a week or two, local anesthetic or/and corticosteroids can be used	- Impetigo [im-puh-TIE-go] is a highly contagious bacterial skin infection that mainly affects infants and children. Impetigo usually appears as red sores on the face, especially around a child's nose and mouth. - The sores burst and develop honey-colored crusts. - Impetigo may clear on its own in two to three weeks, but antibiotics can shorten the course of the disease and help prevent the spread to others.

Shingles

- **Shingles** also *known as* **zona**, is a **viral disease** ***characterized by*** a **painful skin rash** *with* **blisters** in a ***limited*** **area** *on* **one side** of the **body** (**left** or **right**), *often* in a **stripe**.
- **Shingles** is *caused by* the **Varicella Zoster Virus** (**VZV**), the *same* **virus** that *causes* **chickenpox**.
- *After* **chickenpox** ***infection***, the **virus** ***lies inactive*** in **nerve tissue**.
- **Years** ***later***, the **virus** may ***reactivate*** as **shingles**.
- **Causes**;
  - **Shingles** is ***caused by*** the **varicella-zoster virus** (**VZV**) the ***same*** **virus** that *causes* **chickenpox**.
  - ***Anyone*** who's had **chickenpox** *may* ***develop*** **shingles**.
  - ***After*** **recover** *from* **chickenpox**, the **virus** can ***enter*** in the **nervous system** and ***lie*** **dormant** for **years**. *Eventually*, it may ***reactivate*** and **travel** ***along*** **nerve** ***pathways*** to the **skin** → ***producing*** **shingles**.
  - The ***reason*** for the **encore** is ***unclear***, but it may be *due to* ***lowered*** **immunity** to **infections** as in **case** of ***grow*** **older**.
  - **Shingles** is ***more common*** in **older adults** and in **people** who have ***weak*** **immune systems**.



- **Progression** of **herpes zoster**;
  1) A ***cluster*** of **small bumps**.
  2) **Turns** *into* **blisters**.
  3) The **blisters** are ***filled*** and ***break*** **open**.
  4) **Crust** ***over***.
  5) ***Finally*** **disappear**.
- **Transmission**;
  - A **person** *with* **shingles** can ***pass*** the **varicella-zoster virus** to ***anyone*** who **isn't** ***immune*** to **chickenpox**.
  - This ***usually*** occurs through ***direct*** **contact** with the ***open*** **sores** of the **shingles rash**. ***Once*** **infected**, the **person** will ***develop*** **chickenpox**, however, *not* **shingles**.
- **Signs** and **Symptoms**;
  - The **signs** and **symptoms** of **shingles** *usually* ***affect*** **only** a ***small*** **section** of **one side** of the **body**.
  - These **signs** and **symptoms** *may include*:
    - **Pain**, **burning**, **numbness** or **tingling**.
    - A **red rash** that ***begins*** a ***few*** **days** ***after*** the **pain**.
    - **Fluid-filled blisters** that ***break*** **open** and **crust** ***over***.
    - **Itching**.

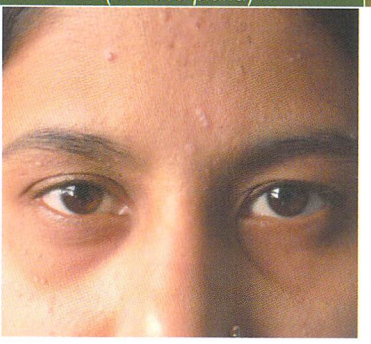
- **Risk factors**; ***anyone*** who has **ever** *had* **chickenpox** *can* ***develop*** **shingles** (before the advent of the routine childhood vaccination that now protects against chickenpox).
  - **Factors** that *may* ***increase*** the **risk** of ***developing*** **shingles** *include*:
    - **Age**: Shingles is most common in people older than 50.
    - **Diseases**: Diseases that weaken the immune system, such as HIV/AIDS.
    - **Cancer Chemotherapy**.
    - **Immunomodulator Medications**:

- **Complications**;
  - **Post-Herpetic Neuralgia** (**PHN**);
    - It occurs when damaged nerve fibers send confused and exaggerated messages of pain from the skin to the brain.
  - **Vision Loss** (Ophthalmic shingles);
    - Can cause painful eye infections that may result in vision loss.
  - **Neurological Problems**:
    - Shingles can cause an inflammation of the brain (encephalitis), facial paralysis, or hearing or balance problems.

- **Treatments**; The **aims** of **treatment** are to ***limit*** the ***severity*** and ***duration*** of **pain**, ***shorten*** the **duration** of a **shingles episode**, and ***reduce*** **complications**.
  - *for* **Shingels**;
    - **Antiviral drugs**; inhibits VZV replication and reduce the severity and duration of herpes zoster with minimal side effects;
      - **Acyclovir** (**Zovirax**®); 200 mg 5 times daily or 400-800 mg 2-4 times daily for 7-10 days.
      - **Valacyclovir** (**Valtrex**®); 1 g orally every 8 hours for 7 days.
      - **Famciclovir** (**Famvir**®); 500 mg orally every 8 hrs; for 7 day.
    - **Analgesics**;
      - ***Mild*** to ***moderate*** **pain**; ***analgesics*** such as **Ibuprofen** and **Naproxen**.
      - **Topical lotions** *containing* **Calamine** can be **used** on the **rash** or **blisters** and ***soothing***.
      - **Numbing agents**, such as **Lidocaine**.
  - *for* **Post-Herpetic Neuralgia** (**PHN**);
    - **Tricyclic Antidepressants** (**TCAs**); **Amitriptyline** and **Nortriptyline**.
    - **Antidepressants**; **Duloxetine** (**Cymbalta**®)
    - **Anticonvulsants**; **Gabapentin** (**Neurontin**®) and **Pregabalin** (**Lyrica**®).
    - **Long-acting Opioids**.
    - **Lidoderm**® **patch**; **Lidocaine** patches.
    - **Transcutaneous Electrical Nerve Stimulation** (**TENS**); a device that generates low-level pulses of electrical current on the skin's surface.

Warts

- **Warts** (**Verrucae**) are ***non-cancerous*** **skin growths** *caused by* a **virus** called the ***Human papillomavirus*** (**HPV**). This **virus** ***causes*** a ***rapid*** **growth** of **cells** on the ***outer layer*** of the **skin**.
- It **typically** *occurs* on ***humans'*** **hands** or **feet** *but often* in ***other*** **locations**.
- **Most Common Types**;

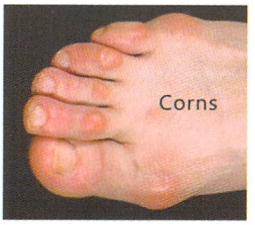
Plantar Wart (*Verruca plantaris*)	Plana or Flat Wart (*Verruca plana*)	Common Wart (*Verruca vulgaris*)
		

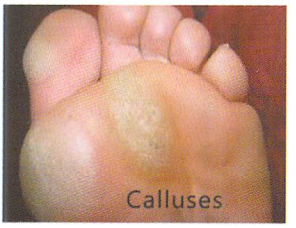
Filiform Wart (*Verruca filiformis*)	Digitate Wart (Verruca digitata)	Genital Wart (*Condyloma acuminatum*)

- **Transmission**; ***Like*** *other* **infectious diseases**, **wart viruses** ***pass*** *from* **person** *to* **person**.
- **Treatments**;
  - **Medications**;
    - **Salicylic acid**; **Collomack®** (Salicylic acid 20%, Lactic acid 5% and Polidocanol 2%).
    - **Imiquimod** (**Aldara®**); Is a topical cream that helps the body's immune system fight the wart.
    - **Cantharidin**, **Bleomycin** and **Dinitrochlorobenzene** (**DNCB**).
  - **Procedures**;
    - **Keratolysis**; is the removal of dead surface skin cells by using keratolytic agents.
    - **Electrodesiccation and curettage**; is a procedure used to treat low-risk tumors and precancerous lesions and warts.
    - **Cryosurgery** or **cryotherapy**; which involves freezing the wart (generally with liquid nitrogen), an average of 3 to 4 treatments are required for warts on thin skin.
    - **Laser treatment**; often with a pulse dye laser or carbon dioxide (CO_2) laser.
- **Differential Diagnosis**;

Calluses and Corns

- They form to protect the skin and structures under the skin from pressure, friction, and injury.
- Treatment by avoiding repetitive actions that caused them to develop and use OTC keratolytic preparations such as Collomack®





Cellulitis and Erysipelas

- They are **acute**, **painful** and ***potentially serious*** **infection** of the **skin** and **subcutaneous tissues**.
- The ***most common*** **causative organisms** are ***Streptococcus*** or ***Staphylococcus*** *spp.*
- ***Treatments***; ***oral*** or ***pareteral*** **antibiotics**; **Penicillin**, **Clindamycin** or **Erythromycin**.

Cellulitis

- Symptoms; redness, swelling, tenderness, pain, warmth and fever.
- Infection of the deep layer of skin (dermis) and the layer of fat and tissues just under the skin (the subcutaneous tissues).
- More commonly seen in the lower limbs and usually affects one limb.

Erysipelas

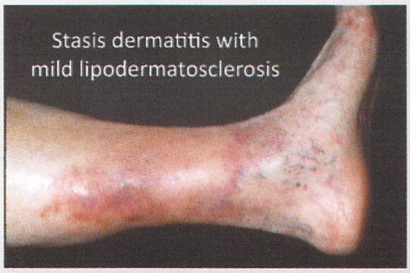
- Symptoms; local oedema, tenderness and warmth, Malaise, chills, and high fever (flu-like symptoms).
- Infection of the skin which is nearer to the skin surface (more superficial) than cellulitis.
- More well-defined edge.
- The face or a leg are commonly affected.
- The arm or upper thigh are the next most common areas to be affected.

- ***Differential Diagnosis***;

Stasis Dermatitis (Varicose Eczema)

- One of the most common signs of Varicose Veins and mostly misdiagnosed by clinics.
- Treatments;

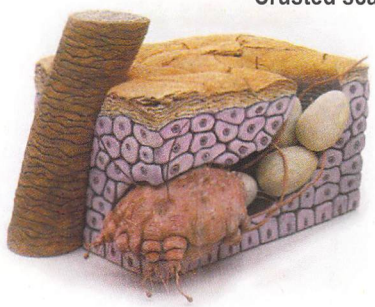
1) Topical corticosteroids & topical (or oral) antihistamines.
2) Emollients.
3) Elevating the legs & compression therapy.
4) Venoactive drugs.
5) Procedure therapy (permanent relief).



Scabies and Lice

- **Scabies** is an ***itchy***, ***highly contagious*** **skin condition** caused by an ***infestation*** by the **itch mite** ***Sarcoptes scabiei***.
- ***Direct*** **skin-to-skin** ***contact*** is the ***mode of transmission***.
- ***Treatment*** includes ***oral*** or ***topical*** **scabicidal drugs**.
- **Crusted scabies** is a ***more severe*** form of the **infection** often *associated with* **immunosuppression** such as **HIV** and **cancer**.

Crusted scabies



- ***Treatments*** of **Scabies**;

Permethrin (Ectomethrin®)# (Elimite®)

- **Permethrin** works by ***paralyzing*** and ***killing*** the **mites** used in **lice** and **scabies**
- ***Formulations***; **cream 5%**, **liquid 1%** and **lotion 1%**.
- **Scabies**; ***Cream***: ***apply*** *from* **head** ***to*** **toe**, *leave on* for **8-14 hours**, rinse; *may* **reapply** in **7 days** if **live mites** ***reappear***.
- **Lice**; *apply to* **washed hair**, *leave on* **10 min**; may ***repeat in*** **7 days** if **lice** still present
- ***Mild infections***; One application is normally sufficient for mild infections.
- ***Moderate*** to ***severe infections***; applied **7-14 days** ***later***.

Ivermectin (Iverzine®)#

- ***Oral*** **Ivermectin**; effective in eradicating scabies, often in a ***single dose***.
- ***Dose*** ***in*** **Scabies**: 0.2 mg (200 mcg)/kg orally once, and repeated in 2 weeks.
- ***Not used*** for **pregnant** and **children** under **six years** of age (***less than*** 15 kg).
- ***Topical*** **Ivermectin** have been found to be ***effective for*** **scabies**.

Crotamiton (Eurax®)#

- ***Applied*** **once** a **day** *for* **2-5 days**.

Benzyl Benzoate (Benzanil®)#

- **Benzyl benzoate** is used to treat **lice** and **scabies** infestations.
- ***Use*** **just one time** (in **severe**, ***repeated*** after **24 hours** ***one time*** anytime ***within*** **5 days**).

- **Lice** are **parasitic** ***insects*** that can be *found on* **people's heads**, and **bodies**, including **pubic area**.

- ***Treatments*** of **Lice**;

Malathion (Quick®)#

- ***Topical*** **Malathion** **0.5%** ***applied*** to **dry hair** and ***washed off*** *after* **8-12 hours**.
- It can be ***re-applied*** if ***live*** **lice** are ***detected after*** **7-10 days**.

Pyrethrins + Piperonyl butoxide (Licide®)#

- The product is applied like a ***shampoo*** to **dry hair** for **10 minutes** and then ***rinsed off*** with **cool water**; ***avoid*** **hot water** causes VD, may ***increase*** **absorption** of **Pyrethrin**.
- Treatment may be repeated if necessary once in a 24-hour period.

Permethrin (Ectomethrin®)#	Benzyl alcohol lotion 5% (Ulesfia®)	Benzyl Benzoate (Benzanil®)

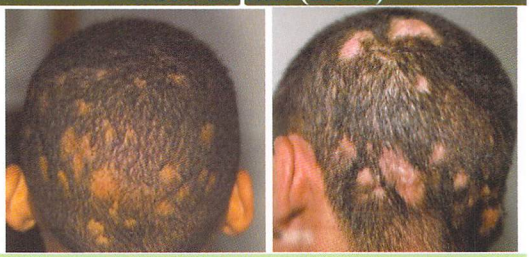
Tinea Infections

- **Dermatophyte infection** (**Ringworm** or **Tinea**) of the body is a ***fungal infection*** that develops on the **top layer** of the **skin**.

Tinea Barbae (Beard)

Fungal infection of the Hair & hair follicles of beard

Tinea Capitis (Head)



Fungal infection of the scalp and hair shafts

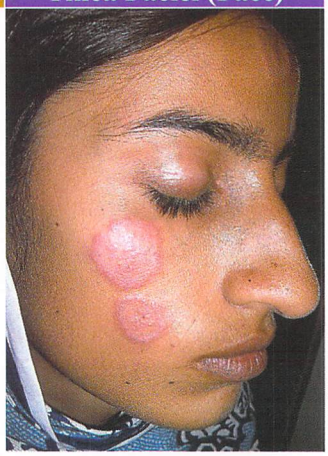
Tinea Corporis (Body)

Circle of rash on the skin that's red and inflamed around the edge and healthy looking in the middle.

Tinea Cruris (Groin)

Fungal infection that affects the skin of the genitals, inner thighs and buttocks.

Tinea Faciei (Face)



Fungal infection of the surface (superficial) skin of the face.

Tinea Manuum (Hand)

Fungal infection of skin in hands

Tinea Pedis (Athlete's Foot)

Fungal infection in the spaces of toes

Tinea Unguium (Nail)

Fungal infection in nails

Treatments; see; **Antifungal** in ***Antimicrobial chapter***

Tinea Versicolor

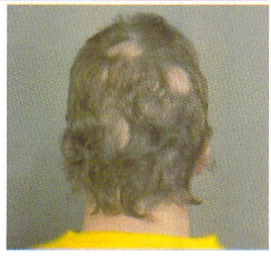
The fungus interferes with the normal pigmentation of the skin, resulting in small, discolored patches.

Pityriasis Rosea (PR)

- **Pityriasis rosea** (**PR**) is a ***skin rash*** that *usually begins as* ***one*** **large circular** or **oval spot** on the **chest, abdomen** or **back**.
- **Pityriasis rosea** can ***affect*** *any age* **group**, but it ***most commonly*** occurs *between* the ages of **10** and **35 years**.
- It ***usually goes away*** on its own ***within*** **6 weeks**.
- **Pityriasis rosea** can *cause* **itching**, and ***treatment*** usually *focuses on* ***relieving*** **symptoms**.
- The ***exact cause*** of pityriasis rosea is ***unclear***, but its clinical presentation and ***immunologic reactions*** suggest a **viral infection** as a cause, Pityriasis rosea, however, ***isn't*** believed to be **contagious**.
- In ***most cases***, **pityriasis rosea** *goes away* on its own in 4-6 **weeks**.
- If the rash ***doesn't*** **disappear** by then or if the itching is bothersome, a variety of treatments can help: **Corticosteroids** and **Antihistamines**: Also can ***reduce*** **itching**.
- **Antiviral drugs**: such as **Acyclovir** (**Zovirax**®) may ***reduce*** the *duration of* **pityriasis rosea** by 1-2 weeks

Hair loss (Alopecia)

1) Alopecia Areata (AA)



- **Alopecia areata** is a condition that causes ***round patches*** of **hair loss**.
- **Alopecia areata** is thought to be an ***autoimmune condition***; this occurs when the **immune system** (***T-Lymphocytes***) ***mistakenly*** **attacks** and **destroys healthy body tissue**.
- **Alopecia areata** is seen in **men**, **women**, and **children**.
- ***Forms of*** **Alopecia areata** include:
  - **Alopecia Areata** → ***Patches*** of **hair** ***loss***.
  - **Alopecia Totalis** → ***Complete loss*** of **scalp hair**.
  - **Alopecia Universalis** → ***Total loss*** of all **body hair**.
- ***Treatments***;
  - If the **alopecia areata** is ***localized*** or ***less than*** 50% → **Topical treatments**.
  - If the **alopecia areata** is ***localized*** or ***higher than*** 50% → **Systemic treatments**.

A) ***Topical treatments***;

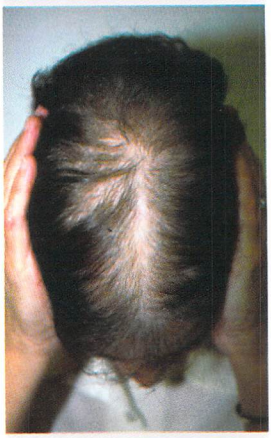
1) ***Topical*** **Corticosteroids**.
   - ***Intralesional injections***; **Triamcinolone Acetonide** (**Kenalog**®); *every* **4-6 weeks**.
   - ***Topical application***; **Betamethasone Dipropionate** (**Diprosone**®); ***twice*** *per* **day**.

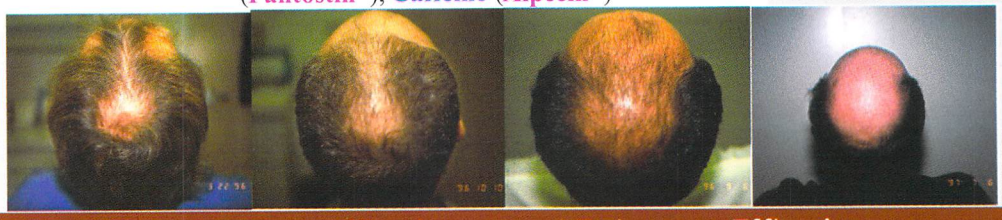
2) ***Topical*** **Immunotherapy**.
   - **Anthralin** or **Dithranol**; (**Psoriatec**®) - (**Dritho-Scalp**®)
   - **Minoxidil** (**Rogaine**®); *applied* ***twice*** **per day**.

B) ***Systemic treatments***;
- ***Systemic Corticosteroids***; **Prednisone** (**Hostacortin**®)
- ***Immunosuppressive Drugs***; **Methotrexate** and **Cyclosporine** (**Sandimmune**®)
- ***Immunomodulator Drugs*** (Biologics); **Infliximab** (**Remicade**®).

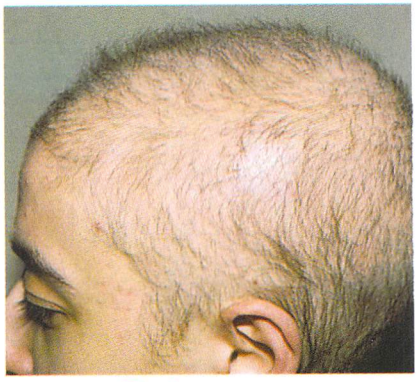
2) Androgenetic Alopecia (AGA)

- **Hair loss** is ***gradual***, with ***miniaturization*** of ***genetically programmed hair follicles***.
  - ***In* female**: **hair loss *occurs*** in the **frontal hairline**.
  - ***In* men**: **hair loss** occurs in the ***fronto-temporal* regions** and on the **vertex** of the **scalp**, *depending on* **severity**.
- ***Treatments***;
  - **Minoxidil (Rogaine®)**;
    - **Topical solution** 2% (*for women*) 5% (*for men*)
    - **Topical foam** 5% (*for sensitive patient*).
    - ***Dose***; Apply 1 ml twice daily.
    - ***Duration***; Hair growth may require **4 months** of therapy; **DON'T *stop* Minoxidil** by yourself.
  - **Finasteride (ProHair®)**; **1 mg** orally for ***at least* 3 months**.
  - ***Other agents***; **Cyproterone + Ethinyl estradiol (Diane-35®)**, **Spironolactone (Aldactone®)**, **Alfatradiol (Pantostin®)**, **Caffeine (Alpecin®)**





3) Anagen Effluvium and Telogen Effluvium



- ***Anagen effluvium***; ***loss*** of **anagen** or ***growth*-phase hairs**; **~90%** of the **hair**.
- It is ***caused by* radiation therapy** to the head and ***systemic* chemotherapy**, especially with **alkylating agents**.

- ***Telogen Effluvium***; ***loss*** of **telogen** or ***growth*-phase hairs**; **~10%** of the **hair**.
- It is ***caused by***; Emotional or physiological stress eating disorders, fever, childbirth, chronic illness, major surgery, anemia, severe emotional disorders, hypothyroidism and drugs.

4) Self-Induced Hair Loss

- Some damage to the hair is self-inflicted sometimes consciously or unconsciously the two main types of self-induced hair loss are Trichotillomania and Traction Alopecia.

Check Yourself

Answers Table; Page No.; 391

Day 1

1) Which of the following listed penicillins is an orally penicillin?

A) Penicillin G
B) Penicillin V
C) Procaine Penicillin
D) Benzyl-penicillin

2) Which of the following brands of Augmentin® is likely to be most effective in the treatment of recurrent or persistent acute otitis media in children; weight is 15 kg?

A) Augmentin® 228
B) Augmentin® 457
C) Augmentin® 375
D) Augmentin® ES-600

3) Which of the following listed 2nd generation cephalosporins available is acceptable taste and is available in strawberry taste in oral formulations?

A) Zinnat®
B) Ceclor®
C) Cefzil®
D) B and C

4) Which of the following 3rd generation cephalosporins is not used in premature neonates?

A) Cefotaxime
B) Ceftriaxone
C) Cefixime
D) Cefoperazone

5) Which of the following is likely to be most correct dose of Suprax® 100 mg/5 mL susp. in children; weight is 17.5 kg?

A) 5 mL orally twice
B) 7 mL orally once
C) 10 mL orally twice
D) 12 mL orally twice

Your Score No. of correct answers	1	2	3	4	5
	❑	❑	❑	❑	❑

Day 2

1) Which of the following drugs is most effective in pseudomembranous colitis?

A) Vancomycin
B) Nystatin
C) Methicillin
D) Ceftriaxone

2) Which of the following β-lactams not cause cross-sensitivity with other β-lactams?

A) Carbenicillin
B) Aztreonam
C) Ticarcillin
D) Cefditoren

3) Which of the following antibiotics is effective in one single dose in UTI?

A) Fosfomycin
B) Cycloserine
C) Vancomycin
D) Daptomycin

4) Which of the following antibiotics is orally effective against MRSA, cSSSI & uSSSI?

A) Tigecycline
B) Linezolid
C) Vancomycin
D) Daptomycin

5) Which of the following antibiotics is likely to be most effective in the treatment of Toxoplasmosis during Pregnancy?

A) Rovamycin®
B) Klacid®
C) Zithromax®
D) Josaxin®

Your Score No. of correct answers	1	2	3	4	5
	❑	❑	❑	❑	❑

Day 3

1) Which of the following antibiotics may cause articular erosion in children?

A) Levofloxacin
B) Telithromycin
C) Azithromycin
D) All of the above

2) Which of the following antibiotics may cause Stevens Johnson syndrome (SJS)?

A) Nalidixic acid
B) Chloramphenicol
C) Co-Trimoxazole
D) Telithromycin

3) Which of the following antibiotics can cause prolong QT interval?

A) Nalidixic acid
B) Chloramphenicol
C) Co-Trimoxazole
D) Levofloxacin

4) Which of the following antibiotics in Zymar® eye drops?

A) Gatifloxacin
B) Moxifloxacin
C) Ciprofloxacin
D) Levofloxacin

5) Which of the following anti-tubercular drug is not used as first line therapy?

A) Rifampicin
B) Isoniazid
C) Ethambutol
D) Pyrazinamide
E) Cycloserine

Your Score No. of correct answers	1 ❑	2 ❑	3 ❑	4 ❑	5 ❑

Day 4

1) Which of the following antifungal is a drug of choice for the treatment of several life-threatening mycoses?

A) Amphotericin B
B) Itraconazole
C) Griseofulvin
D) Terbinafine

2) Which of the following antifungal is a drug of choice for the treatment of Dermatophytosis?

A) Amphotericin B
B) Itraconazole
C) Nystatin
D) Terbinafine

3) Loceryl® and Exoderil® are common antifungal brands used for;

A) Ringworm
B) Onychomycosis
C) Athlete's foot
D) Tinea cruris

4) Which of the following antiviral brands can be used for influenza A infections?

A) PK-Merz®
B) Valtrex®
C) Zeffix®
D) Sovaldi®

5) Ribavirin is category X and should be avoided before 6 months of planning to pregnancy in;

A) Men
B) Women
C) Both men and women

Your Score No. of correct answers	1 ❑	2 ❑	3 ❑	4 ❑	5 ❑

Day 5

1) Augmentin® XR tablets is effective in the treatment of community acquired pneumonia, acute exacerbations of chronic bronchitis and acute bacterial sinusitis in dose?

A) 2 tablets every 24 hours
B) 2 tablets every 12 hours
C) 1 tablets every 24 hours
D) 1 tablets every 12 hours

2) Which of the following brands of Azithromycin least affected by food?

A) Zithromax®
B) Xithrone®
C) Zisrocin®
D) Zithrokan®

3) Which of the following antibiotics is likely to be most effective as a single dose in the treatment of Chlamydia Infection?

A) Levofloxacin
B) Ofloxacin
C) Azithromycin
D) Doxycycline

4) Which of the following antibiotics may prolong QT interval?

A) Levofloxacin
B) Telithromycin
C) Azithromycin
D) All of the above

5) Lariam® is an antimalarial agent commonly used in prophylaxis in dose;

A) 250 mg once weekly
B) 250 mg twice weekly
C) 500 mg once weekly
D) 500 mg twice weekly

Your Score No. of correct answers	1 ❑	2 ❑	3 ❑	4 ❑	5 ❑

Day 6

1) Which of the following antacid brands contain physical barrier to acid?

A) Maalox®
B) Epicogel®
C) Mucogel®
D) Gaviscon®

2) H_2RAs has marked effect on;

A) Nocturnal acid secretion
B) Meal-stimulated secretion
C) Both

3) Which of the following supplements Patients may needed during long term use of PPIs?

A) Vitamin B_{12}
B) Iron
C) Calcium and Magnesium
D) All of the above

4) *H. Pylori* treatment include all the following Except;

A) Metronidazole
B) Clarithromycin
C) Amoxicillin
D) Tetracycline
E) Vancomycin

5) Motilium® 30 mg supp is avoided in children < 10 years due to;

A) Fatal QT prolongation
B) Extrapyramidal symptoms
C) Tardive dyskinesia
D) Increase Prolactin

Your Score No. of correct answers	1 ❑	2 ❑	3 ❑	4 ❑	5 ❑

Day 7

1) Which of the following is correct about concentration of Zofran® 4 mg ampoules?

A) Same as Zofran® 8 mg B) Double of Zofran® 8 mg C) Half of Zofran® 8 mg

2) Which of the following antiemetic brands can cause acute systemic toxicity, if used in pediatrics in full ampoule dose?

A) Zofran® 2mL
B) Emetrex®
C) Cortigen-B6®
D) Depo-Medrol®

3) Role of Atropine in Lomotil® is;

A) Decrease GI motility
B) Synergistic effect
C) Discourage abuse
D) Increase GI motility

4) Antimotility agents is contraindicated in

A) High fever
B) Bloody stool
C) Black stool
D) All of the above

5) Which of the following laxatives act after 12-72 hours?

A) Meta-mucil®
B) Picolax®
C) Dulcolax®
D) Senokot®

Your Score No. of correct answers	1 ❑	2 ❑	3 ❑	4 ❑	5 ❑

Day 8

1) Which of the following digestive and/or antispasmodic brands contraindicated in lactating women?

A) Buscopan®
B) Visceralgine®
C) Do-Spa®
D) Spasmo-digestin®

2) Which of the following brands of Mebeverine contain one of two components of Librax®?

A) Duspatalin®
B) Coloverin® SR
C) Coloverin®-D
D) Coloverin®-A

3) Which of the following brands contain Mesalamine and used for Inflammatory Bowel Disease (IBD)?

A) Pentasa®
B) Canasa®
C) Rowasa®
D) All of the above

4) Which of the following TNF-α inhibitors brands contain Infliximab?

A) Remicade®
B) Humira®
C) Cimzia®
D) Simponi®

5) Which of the following brands contain Ursodiol and used in Cholelithiasis?

A) Rowachol®
B) Rowatinex®
C) Ursofalk®

Your Score No. of correct answers	1 ❑	2 ❑	3 ❑	4 ❑	5 ❑

Day 9

1) Which of the following H_2RAs most potent?

A) Cimetidine
B) Ranitidine
C) Nizatidine
D) Famotidine

2) Sodium Bicarbonate in Zegerid® was added to;

A) Protect Omeprazole from acid degradation
B) Increase Omeprazole solubility
D) Act as antacid
C) Decrease Omeprazole drug interactions

3) Which of the following antiemetic brands are used as first line in NVP?

A) Diclegis®
B) Epidron®
C) Zofran®
D) Primperan®

4) Which of the following antimicrobials is good choice in traveler's diarrhea for pregnant women and children?

A) Zithromax®
B) Tavanic®
C) Vibramycin®
D) Septrin®

5) Which of the following antidiarrheal agents act as antisecretory?

A) Kaolin-Pectin
B) Methylcellulose
C) Racecadotril
D) Cholestyramine

Your Score No. of correct answers	1 ❑	2 ❑	3 ❑	4 ❑	5 ❑

Day 10

1) Which of the following brands of second generation antihistamines is partially sedating?

A) Claritin®
B) Zyrtec®
C) Telfast®
D) Semprex®

2) Which of the following brands of antihistamines used off-label as an appetite stimulant?

A) Avil®
B) Donormyl®
C) Triactin®
D) Betaserc®

3) Which of the following brands of antihistamines is most likely used in insomnia?

A) Avil®
B) Donormyl®
C) Triactin®
D) Betaserc®

4) Which of the following brands of antihistamines is most likely used in Ménière's disease?

A) Avil®
B) Donormyl®
C) Triactin®
D) Betaserc®

5) Which of the following brands of antihistamines is most likely used in dry chough?

A) Anallerge®
B) Claritin®
C) Telfast®
D) Aerius®

Your Score No. of correct answers	1 ❑	2 ❑	3 ❑	4 ❑	5 ❑

Day 11

1) Which of the following brands is SABA?

A) Ventolin®
B) Serevent®
C) Foradil®
D) Onbrez®

2) Which of the following brands is Ultra-LABA?

A) Ventolin®
B) Serevent®
C) Foradil®
D) Onbrez®

3) Which of the following statements is correct about Foradil®?

A) Used for acute asthma
B) Used without ICS in chronic asthma
C) May used as monotherapy for COPD
D) None of the above

4) Which of the following bronchodilators has low therapeutic index?

A) Quibron®
B) Serevent®
C) Spiriva®
D) Atrovent®

5) Which of the following leukotriene modifiers not cause hepatotoxicity?

A) Zafirlukast
B) Montelukast
C) Zileuton

Your Score No. of correct answers	1 ❑	2 ❑	3 ❑	4 ❑	5 ❑

Day 12

1) Which of the following brands of antihistamines is most likely used in Allergic rhinitis?

A) Anallerge®
B) Donormyl®
C) Aerius®
D) Avil®

2) Intranasal Corticosteroids are the first line therapy in

A) Mild allergic rhinitis
B) Moderate allergic rhinitis
C) Severe allergic rhinitis
D) B and C

3) Which of the following agents can cause rhinitis medicamentosa in long term use?

A) Oxymetazoline
B) Cromolyn
C) Azelastine
D) Ipratropium

4) Which of the following antitussives is act as peripheral cough reflex inhibitors?

A) Dextromethorphan
B) Benzonatate
C) Noscapine
D) Butamirate

5) Which of the following NSAIDs is recommended in the guidelines for treatment of cough associated with common cold?

A) Naproxen
B) Ibuprofen
C) Paracetamol
D) Diclofenac

Your Score No. of correct answers	1 ❑	2 ❑	3 ❑	4 ❑	5 ❑

Day 13

1) Which of the following brands of antihistamines act as mast cell stabilizing effects in addition to their H1-blocking effects.

A) Anallerge®
B) Aerius®
C) Zaditen®
D) Claritin®

2) Which of the following ICS brands is prodrug and may cause fewer local side effects?

A) Alvesco®
B) Miflonide®
C) Azmacort®
D) Flixotide®

3) Local side effects of ICS such as oral candidiasis and hoarseness can be minimized by;

A) Deeply once inhalation in each dose
B) Inhalation just after meal
C) Gargle water and spit after each inhaled
D) Inhalation just before meal

4) Which of the following brands act as anti-IgE and used in allergic asthma?

A) Zyflo®
B) Xolair®
C) Intal®
D) Accolate®

5) Usual dose of Champix® in day no. 10 in quit smoking course in adult is;

A) 0.5 mg orally once a day.
B) 0.5 mg orally twice a day.
C) 1 mg orally once a day
D) 1 mg orally twice a day

Your Score No. of correct answers	1 ❑	2 ❑	3 ❑	4 ❑	5 ❑

Day 14

1) Which of the following Hormones synthesized form DHEA?

A) Oxytocin
B) Dopamine
C) Serotonin
D) Testosterone

2) Which of the following brands used for the treatment of Hypoactive Sexual Desire Disorder (HSDD) in pre-menopausal women.

A) Viagra®
B) Addyi®
C) Caverject®
D) Yohimbex®

3) Which of the following PDE-5 inhibitors has shorter duration of action?

A) Viagra®
B) Levitra®
C) Stendra®
D) Cialis®

4) Which of the following brands is more effective for premature ejaculation

A) Anafranil®
B) Joybox®
C) Cipralex®
D) Seroxat®

5) Which of the following agents is most effective to treat Trichomoniasis?

A) Doxycycline
B) Metronidazole
C) Clindamycin
D) Fluconazole

Your Score No. of correct answers	1 ❑	2 ❑	3 ❑	4 ❑	5 ❑

Day 15

1) Citrate Therapy is used in calcium oxalate stones due to Citrate act as;

A) Alkalinizing agent
B) Acidifying agent
C) Form soluble complex
D) A and C

2) Struvite stones in urine are indicate to;

A) Infections
B) Acidic urine
C) Alkaline urine

3) Which of the following NSAIDs brands used as drug of choice in renal colic pain?

A) Voltaren®
B) Brufen®
C) Panadol®
D) Celebrex®

4) Which of the following brands may cause floppy iris syndrome during cataract surgery?

A) Cardura®
B) Flomax®
C) Rapaflo®
D) Xatral®

5) Which of the following agents act in adrenergic receptors to relax the detrusor muscles of the bladder to treat urinary incontinence?

A) Solifenacin
B) Mirabegron
C) Desmopressin
D) Finasteride

Your Score No. of correct answers	1 ❑	2 ❑	3 ❑	4 ❑	5 ❑

Day 16

1) Which of the following agents if used with Flibanserin may increases the risk of severe hypotension and syncope?

A) Tyramine food
B) Nitrates
C) Alcohol
D) Nicotine

2) Which of the following PDE-5 inhibitors available in an orally disintegrating tablet?

A) Avanafil
B) Vardenafil
C) Tadalafil
D) Sildenafil

3) Which of the following brands may off-label used in retarded ejaculation?

A) Triactin®
B) Contramal®
C) Avodart®
D) Dexazone®

4) 5-α-Reductase inhibitors are most beneficial if the prostates larger than;

A) 10 g
B) 20 g
C) 30 g
D) 40 g

5) Duodart® brand contain combination of;

A) Finasteride + Tamsulosin
B) Dutasteride + Tamsulosin
C) Finasteride + Silodosin
D) Dutasteride + Silodosin

Your Score No. of correct answers	1 ❑	2 ❑	3 ❑	4 ❑	5 ❑

Day 17

1) Which of the following NSAIDs is not contraindicated in patients with high risk for cardiovascular events?

A) Ibuprofen
B) Naproxen
C) Diclofenac
D) None of the above

2) Which of the following brands can overcome NSAID-associated bronchospasm?

A) Singulair®
B) Miflonide®
C) Ventolin®
D) None of the above®

3) NSAIDs should be used at the;

A) Lowest effective dose
B) Highest effective dose
C) Shortest possible duration of therapy
D) A and C

4) Which of the following brands may be beneficial in pregnancies to decrease the risk of pre-eclampsia?

A) Jusprin®
B) C-Retard®
C) Omega-3®
D) B and C

5) Which of the following statements is correct about Acetaminophen?

A) American name of Paracetamol
B) Active metabolite of Paracetamol
C) Prodrug of Paracetamol
D) None of the above

Your Score No. of correct answers	1 ❑	2 ❑	3 ❑	4 ❑	5 ❑

Day 18

1) Which of the following brands is one of the most widely synthetic opioids used and available in different types of formulations?

A) Duragesic®
B) Dilaudid®
C) Dolophine®
D) Demerol®

2) Naloxone in Talwin® and Suboxone® is added to;

A) Discourage abuse
B) Synergistic effect
C) Decrease withdrawal symptoms
D) B and C

3) Lofexidine (Detoxydine®) is added in opioid detoxification regimens due to it act as;

A) Opioid Antagonist
B) Opioid Agonist
C) α_2 Agonist
D) Serotonin Agonist

4) Which of the following antispasticity agents act as $GABA_B$ receptors?

A) Diazepam
B) Baclofen
C) Tizanidine
D) None of the above

5) Which of the following brands may cause serious hepatocellular toxicity especially in liver impairment?

A) Norflex®
B) Sirdalud®
C) Myofen®
D) Myolgin®

Your Score No. of correct answers	1 ❑	2 ❑	3 ❑	4 ❑	5 ❑

Day 19

1) Which of the following NSAIDs has been historically favored as NSAID of choice for acute gout?

A) Ibuprofen
B) Naproxen
C) Sulindac
D) Indomethacin

2) Colchicine was historically used in acute gout in;

A) Lower dose
B) Higher doses until GI symptoms

3); Which of the following xanthine oxidase inhibitors act as direct non-competitively blocking effect?

A) Allopurinol
B) Febuxostat

4) Which of the following DMARDs is an abortifacient agent?

A) Methotrexate
B) Etanercept
C) Sulfasalazine
D) Adalimumab

5) Brand of Infliximab is;

A) Remicade®
B) Humira®
C) Simponi®
D) Cimzia®

Your Score No. of correct answers	1 ❑	2 ❑	3 ❑	4 ❑	5 ❑

Day 20

1) Glucosamine may increase risk of;

A) Bleeding
B) Hypertension
C) Blood glucose levels
D) All of the above

2) Which of the following brands of Vitamin D used as a single dose once a year?

A) Sterogyl®
B) Devarol-S®
C) One-Alpha®
D) Vi-De 3®

3) Bisphosphonates esophagitis can be reduced by;

A) Taken with 240 mL of mineral water
B) Taken 30 minutes before food
C) Patient should be remain upright
D) B and C
E) All of the above

4) Premarin® is a;

A) Conjugated Estrogens
B) Conjugated Progestins
C) Conjugated Testosterone

5) Forteo® dose is;

A) 20 mcg SC once a day
B) 60 mcg SC once a day
C) 100 mcg SC once a day
D) 150 mcg SC once a day

Your Score No. of correct answers	1 ❑	2 ❑	3 ❑	4 ❑	5 ❑

Day 21

1) Which of the following brands of NSAIDs is a good choice in primary dysmenorrhoea?

A) Mobic®
B) Celebrex®
C) Ketolac®
D) Ponstan®

2) Maximum single dose of Paracetamol in healthy adults is:

A) 500 mg
B) 1 gm
C) 2 gm
D) 4 gm

3) Which of the following eye drops can be abused by mixing it with Heroin?

A) Toprex®
B) Mydriacyl®
C) Lumigan®
D) Patanol®

4) Which of the following application of Botox® is correct?

A) Prevent development of wrinkles
B) Muscle spasticity
C) Chronic migraine
D) All of the above

5) Which of the following is the most common serious side effects of Plaquenil®?

A) Hepatotoxicity
B) Ocular toxicity
C) Ototoxicity
D) Nephrotoxicity

Your Score No. of correct answers	1 ❑	2 ❑	3 ❑	4 ❑	5 ❑

Day 22

1) Hypokalemia and metabolic alkalosis is the most common side effects of;

A) Amiloride
B) Hydrochlorothiazide
C) Mannitol
D) Spironolactone

2) Which of the following should be avoided in a patient with a history of severe anaphylactic reaction to sulfa medications?

A) Amiloride
B) Hydrochlorothiazide
C) Mannitol
D) Spironolactone

3) β-blockers must be tapered off gradually to avoid;

A) angina or hypertension
B) Hypotension and syncope
C) Arrhythmia
D) Withdrawal symptoms

4) Which of the following ACEIs is contraindicated in patient with sulfa allergy?

A) Capoten®
B) Zestril®
C) Coversyl®
D) Tritace®

5) Dry persistent cough associated with ACEIs can be resolved by;

A) Ferrous sulfate
B) Aspirin
C) Vitamin C
D) A and B

Your Score No. of correct answers	1 ❑	2 ❑	3 ❑	4 ❑	5 ❑

Day 23

1) All of the following antihypotensive drugs are sympathomimetic; Except;

A) Effortil®
B) Gutron®
C) Corasore®
D) Astonin-H®

2) Which medication should be prescribed to all anginal patients to treat an acute attack?

A) Isosorbide dinitrate
B) Nitroglycerin patch
C) Nitroglycerin sublingual tablet or spray
D) Ranolazine

3) Which of the following is a first cytoprotective anti-ischemic agent?

A) Ranexa®
B) Vastarel® MR
C) Procoralan®
D) Randil®

4) Which is important to monitor in patients taking digoxin?

A) Chloride
B) Potassium
C) Sodium
D) Zinc

5) Which of the following is the most common side effect associated with fixed-dose hydralazine/isosorbide (BiDil®) dinitrate?

A) Diarrhea
B) Drug-induced lupus
C) Headache
D) Heartburn

Your Score No. of correct answers	1 ❑	2 ❑	3 ❑	4 ❑	5 ❑

Day 24

1) Which of the following antiarrhythmic drug is mostly like to cause dry mouth, blurred vision and urinary hesitancy?

A) Metoprolol
B) Disopyramide
C) Dronedarone
D) Sotalol

2) All of the following are adverse effects of amiodarone except;

A) Cinchonism
B) Hypothyroidism
C) Hyperthyroidism
D) Pulmonary fibrosis

3) Which arrhythmia can be treated with lidocaine?

A) Atrial fibrillation
B) Atrial fibrillation
C) Supraventricular tachycardia
D) Ventricular tachycardia

4) Which of the following is a non-iodinated benzofuran derivative?

A) Dronedarone
B) Amiodarone
C) Sotalol
D) Dofetilide

5) Lidocaine is an antiarrhythmic and it is classified as

A) Class IA
B) Class IB
C) Class IC

Your Score No. of correct answers	1 ❑	2 ❑	3 ❑	4 ❑	5 ❑

Day 25

1) Which must heparin bind to in order to exert its anticoagulant effect?

A) GP IIb/IIIa receptor
B) Thrombin
C) Antithrombin III
D) von Willebrand factor

2) Protamine sulfate is a Heparin antidote, While Idarucizumab (Praxbind®) is an antidote for;

A) Pradaxa®
B) Argatroban®
C) Angiomax®
D) Xarelto®

3) Which of the following drugs accelerates the conversion of plasminogen to plasmin?

A) Heparin
B) Warfarin
C) Argatroban
D) Reteplase

4) Bioavailability of Dabigatran Etexilate is increased up to 75%, if capsules;

A) Taken in empty stomach
B) Opened and pellets taken alone
C) Taken with food stomach
D) Taken with grapefruit juice

5) Which of the following fibrinolytics is a human plasminogen and bacterial streptokinase?

A) Urokinase
B) Anistreplase
C) Alteplase
D) Reteplase

Your Score No. of correct answers	1 ❑	2 ❑	3 ❑	4 ❑	5 ❑

Day 26

1) Which one of the following drugs decreases cholesterol synthesis by inhibiting the enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase?

A) Fenofibrate
B) Niacin
C) Cholestyramine
D) Lovastatin

2) Pregnant hyperlipidemia patients, which of the following drugs should be avoided because of a risk of harming the fetus?

A) Cholestyramine
B) Ezetimibe
C) Fenofibrate
D) Pravastatin

3) Which of the following is a major toxicity associated with gemfibrozil therapy?

A) Bloating and constipation
B) Cholelithiasis
C) Hyperuricemia
D) Liver damage

4) Which of the following options can help patient to manage this adverse effect of niacin therapy?

A) Used aspirin 30 min. before niacin
B) Used aspirin 30 min. after niacin
C) Increase dose of niacin SR to 1000 mg
D) Continue the current dose of niacin

5) Coenzyme Q10 can be used in patient taking statins to decrease;

A) Cholelithiasis
B) Rhabdomyolysis
C) Hepatotoxicity
D) Hemolysis

Your Score No. of correct answers	1 ❑	2 ❑	3 ❑	4 ❑	5 ❑

Day 27

1) Which of the following diuretics has a unique mechanism of action?

A) Natrilix® SR
B) Zaroxolyn®
C) Esidrix®
D) Burinex®

2) Which of the following is an antianginal drug that has the dual properties of a nitrate and potassium channel activators?

A) Procoralan®
B) Randil®
C) Vastarel® MR
D) Ranexa®

3) Chromatopsia is a common side effects of;

A) Inocor®
B) Lanoxin®
C) BiDil®
D) Digibind®

4) In 2009, the FDA issued a public-health warning about the possible interaction between Clopidogrel and Omeprazole. Which of the following CYP450 isoenzymes is most included in this interactions?

A) CYP3A4
B) CYP2C19
C) CYP2C18
D) CYP1A2

5) Which of the following brands act as phosphodiesterase inhibitor and affects blood rheology?

A) Doxium®
B) Reparil®
C) Trental®
D) Daflon®

Your Score No. of correct answers	1	2	3	4	5
	❑	❑	❑	❑	❑

Day 28

1) Which one of the following is a short-acting hypnotic?

A) Phenobarbital
B) Diazepam
C) Chlordiazepoxide
D) Triazolam

2) Which of the following sedative–hypnotic agents utilizes melatonin receptor agonist as the mechanism of action to induce sleep?

A) Zolpidem
B) Eszopiclone
C) Ramelteon
D) Suvorexant

3) Which of the following sedative–hypnotic agent act as orexin antagonists as the mechanism of action to induce sleep?

A) Zolpidem
B) Eszopiclone
C) Ramelteon
D) Suvorexant

4) This drug used in the management of insomnia facilitates the inhibitory actions of GABA, but it lacks anticonvulsant or muscle-relaxing properties and has minimal effect on sleep architecture.

A) Buspirone
B) Eszopiclone
C) Ramelteon
D) Phenobarbital

5) Which of the following is an antidote for benzodiazepines

A) Anexate®
B) Buspar®
C) Rozerem®
D) Belsomra®

Your Score No. of correct answers	1	2	3	4	5
	❑	❑	❑	❑	❑

Day 29

1) Which of the following antidepressants should be avoided in this patient with angle-closure glaucoma?

A) Amitriptyline
B) Sertraline
C) Bupropion
D) Mirtazapine

2) Which antidepressant is the most sedating?

A) Cymbalta®
B) Wellbutrin®
C) Trittico®
D) Cipralex®

3) SSRIs are much less effective than tricyclic antidepressants in the management of

A) Bulimia
B) Chronic pain of neuropathic origin
C) Generalized anxiety disorder
D) Obsessive-compulsive disorder

4) Which of the following SSRIs has much longer half-life?

A) Fluoxetine
B) Sertraline
C) Citalopram
D) Escitalopram

5) Which agent is best known to have the side effect of decreasing the thyroid function of the patient being chronically treated with this agent?

A) Carbamazepine
B) Lithium
C) Valproic acid
D) Chlorpromazine

Your Score No. of correct answers	1 ❑	2 ❑	3 ❑	4 ❑	5 ❑

Day 30

1) Which of the following agents is wakefulness-promoting?

A) Modafinil
B) Atomoxetine
C) Clonidine
D) Guanfacine

2) Which of the following antipsychotic agents may have the best chance to improve his apathy and blunted affect?

A) Neurazine®
B) Haldol®
C) Clopixol®
D) Risperdal®

3) Which of the following is the most common side effects of Clozapine?

A) Hair loss
B) Anemia
C) Thrombocytopenia
D) Agranulocytosis

4) Which antipsychotic agent has been most associated with significant QT interval prolongation?

A) Thioridazine
B) Risperidone
C) Aripiprazole
D) Lurasidone

5) Which of the following antipsychotic agents is available in a LAI (long-acting injectable) formulation?

A) Asenapine
B) Clozapine
C) Quetiapine
D) Risperidone

Your Score No. of correct answers	1 ❑	2 ❑	3 ❑	4 ❑	5 ❑

Day 31

1) Which one of the following combinations of antiparkinsonian drugs is an appropriate treatment plan?

A) Amantadine, Carbidopa & Entacapone
B) Levodopa, Carbidopa & Entacapone
C) Pramipexole, Carbidopa & Entacapone
D) Ropinirole, Selegiline & Entacapone

2) Which of the following antiparkinsonian drugs may cause vasospasm?

A) Amantadine
B) Bromocriptine
C) Carbidopa
D) Entacapone

3) Modest improvement in the memory of patients with Alzheimer's disease may occur with drugs that increase transmission at which of the following receptors?

A) Serotonergic
B) Dopaminergic
C) Cholinergic
D) Adrenergic

4) Which of the following agents is available as a patch for once-daily use and is likely to provide steady drug levels to treat Alzheimer's disease?

A) Rivastigmine
B) Donepezil
C) Memantine
D) Galantamine

5) Which of the following tests is needed during Gilenya® therapy to monitoring it is side effects?

A) CRP
B) EEG
C) CBC
D) ECG

Your Score No. of correct answers	1 ❑	2 ❑	3 ❑	4 ❑	5 ❑

Day 32

1) Which of the following antiepileptics would be effective in children without the disadvantages of excessive sedation or tolerance development?

A) Diazepam
B) Ethosuximide
C) Gabapentin
D) Phenobarbital

2) Which of the following drugs is most useful for the treatment of absence seizures?

A) Topiramate
B) Tiagabine
C) Levetiracetam
D) Lamotrigine

3) With chronic use in seizure states, the adverse effects of this drug include coarsening of facial features, hirsutism and gingival hyperplasia.

A) Carbamazepine
B) Ethosuximide
C) Phenytoin
D) Tiagabine

4) Neural tube defects may occur with which of the following antiseizure drugs?

A) Ethosuximide
B) Vigabatrin
C) Phenobarbital
D) Valproic acid

5) The preferred treatment of status epilepticus is intravenous administration of;

A) Chlorpromazine
B) Diazepam
C) Succinylcholine
D) Tranylcypromine

Your Score No. of correct answers	1 ❑	2 ❑	3 ❑	4 ❑	5 ❑

Day 33

1) All of the following brands that can used in acute attacks of migraine contraindicated in patients with coronary artery disease, Except;

A) Tylenol® No.3
B) Imitrex®
C) Zomig®
D) Ergomar®

2) Cefaly® device is a transcutaneous electrical nerve stimulation device that is used in;

A) Migraine Acute Attacks
B) Migraine Prophylaxis
C) Status Migrainosus
D) Tension-type Headache

3) Which of the following is a potent analgesic but a weak anesthetic?

A) Etomidate
B) Halothane
C) Midazolam
D) Nitrous oxide

4) Which one of the following is a potent intravenous anesthetic but a weak analgesic?

A) Propofol
B) Ketamine
C) Fentanyl
D) Isoflurane

5) A vasoconstrictor added to a solution of lidocaine for a peripheral nerve block will

A) Reduce bleeding
B) Increase the duration of local anesthetic
C) Both A and B
D) Neither A nor B

Your Score No. of correct answers	1 ❑	2 ❑	3 ❑	4 ❑	5 ❑

Day 34

1) Which one of the following is a short-acting hypnotic and better for sleep induction compared to sleep maintenance?

A) Lorazepam
B) Diazepam
C) Zaleplon
D) Eszopiclone

2) Which of the following brands of SSRIs is indicated only for obsessive-compulsive disorder (OCD)?

A) Prozac®
B) Lustral®
C) Seroxat®
D) Faverin®

3) The risk of Wellbutrin® seizures can be minimized by the following;

A) Dosage titration every 2 days.
B) Not less than 150 mg/dose or 450 mg/day.
C) Both A and B
D) Neither A nor B

4) Which of the following brands may cause livedo reticularis?

A) PK-Merz®
B) Parkinol®
C) Stalevo®
D) Apokyn®

5) Which of the following anticonvulsant are now widely abused?

A) Lamictal®
B) Depakene®
C) Trileptal®
D) Lyrica®

Your Score No. of correct answers	1 ❑	2 ❑	3 ❑	4 ❑	5 ❑

Day 35

1) All of the following hormones brands misused as performance enhancement in athletes, Except;

A) Norditropin®
B) Cidoteston®
C) Deca-Durabolin®
D) Sandostatin®

2) Which of the following agents used off-labeled in esophageal variceal bleeding?

A) Octreotide
B) Somatropin
C) Menotropin
D) Carbetocin

3) Dose of Dostinex® in reduce prolactin levels is;

A) 1 mg on the first day after delivery.
B) 0.25 mg every 12 hours for two days.
C) 0.5 mg/week spread out over a week

4) All of the following hormones brands used in preparation for In Vitro Fertilization (IVF), Except;

A) Pregnyl®
B) Merional®
C) Decapeptyl®
D) Depo-Provera®

5) Which of the following is brands used in the treatment of hyperthyroidism?

A) Neo-Mercazole®
B) Eltroxin®
C) Thyrolar®
D) Cytomel®

Your Score No. of correct answers	1 ❑	2 ❑	3 ❑	4 ❑	5 ❑

Day 36

1) To decrease risk of suppress endogenous corticosteroids secretions; Which of the following is the BEST TIME to take daily dose of systemic corticosteroids?

A) 6-8 AM
B) 6-8 PM
C) 1-4 AM
D) 1-4 PM

2) Systemic corticosteroids are used in 3rd trimester of pregnancy to promoting maturation of fetal lung due to;

A) Production of β_2-receptors
B) Production of surfactant
C) Decrease lung secretion
D) Decrease lung spasm

3) Which of the following statements is correct regarding Lantus®?

A) It is a "peakless" insulin
B) Control postprandial hyperglycemia.
C) Prolonged duration due to long-chain fatty acids.
D) It may be administered IV

4) Which of the following brands for diabetes would be least likely to cause weight gain?

A) Amaryl®
B) Victoza®
C) NovoNorm®
D) Actos®

5) Metformin dose in type 2 DM is;

A) Minimum tolerated dose
B) Maximum tolerated dose
C) 1000 mg/day
D) 850 mg/day

Your Score No. of correct answers	1 ❑	2 ❑	3 ❑	4 ❑	5 ❑

Day 37

1) All of the following are side effects of Estrogens, Except;

A) Na^+ and water retention
B) Breasts tenderness
C) Weight gain
D) Acne and hirsutism

2) Which of the following brands contain Progestin has potent mineralocorticoid antagonist?

A) Yasmin®
B) Cilest®
C) Microlut®
D) Minulet®

3) All of the following agent are abortifacient agent, Except;

A) Mifepristone
B) Methotrexate
C) Misoprostol
D) Levonorgestrel

4) Which of the following brands is Emergency Contraceptive?

A) Microlut®
B) Contraplan II®
C) Depo-Provera®
D) None of the above

5) Ortho Evra® is

A) Contraceptive Patch
B) Contraceptive Vaginal ring
C) Contraceptive Implants
D) None of the above

Your Score No. of correct answers	1 ❑	2 ❑	3 ❑	4 ❑	5 ❑

Day 38

1) Which of the following is the route of administration of Syntocinon® in induction of labor?

A) IM
B) SC
C) IV infusion
D) IV bolus

2) Which of the following brands of corticosteroids is faster in onset of action?

A) Solu-Cortef®
B) Hostacortin®
C) Solu-Medrol®
D) Diprofos®

3) SGLT2 Inhibitors are contraindicated in patients with

A) eGFR <60 mL/min/1.73 m^2
B) eGFR <30 mL/min/1.73 m^2
C) eGFR >60 mL/min/1.73 m^2
D) eGFR >30 mL/min/1.73 m^2

4) Dose of Clomid® is

A) 1 tab. (50 mg) daily for 5 days, starting from the 5th day of woman's cycle.
B) 1 tab. (50 mg) daily for 5 days, starting from the 1st day of woman's cycle.

5) Depo-Provera® injection are repeated every;

A) 1 months
B) 3 months
C) 6 months
D) 8 months

Your Score No. of correct answers	1 ❑	2 ❑	3 ❑	4 ❑	5 ❑

Day 39

1) Which drug in the ABVD regimen is the most likely cause of his pulmonary toxicity?

A) Doxorubicin (Adriamycin)
B) Bleomycin
C) Vinblastine
D) Dacarbazine

2) Which of the following brands is associated with hemorrhagic cystitis?

A) Endoxan®
B) Leukeran®
C) Purinethol®
D) Adrucil®

3) Which of the following agents is associated with interstitial pulmonary fibrosis?

A) Cisplatin
B) Doxorubicin
C) Busulfan
D) Paclitaxel

4) Abraxane® (Paclitaxel) is not associated with hypersensitivity reactions and neurotoxicity than Taxol® (Paclitaxel) due to;

A) Sustained release formulation
B) Albumin-bound formulation
C) Micronized formulation
D) A and C

5) Nexavar® and Sutent® are used in;

A) Renal cell carcinoma
B) Colorectal cancer
C) Chronic myelogenous leukemia
D) None of the above

Your Score No. of correct answers	1 ❑	2 ❑	3 ❑	4 ❑	5 ❑

Day 40

1) Which of the following drugs used to prevent allograft rejection can cause hyperlipidemia?

A) Tacrolimus
B) Belatacept
C) Mycophenolate Mofetil
D) Sirolimus

2) Which of the following drugs specifically inhibits calcineurin in the activated T lymphocytes?

A) Tacrolimus
B) Belatacept
C) Mycophenolate Mofetil
D) Sirolimus

3) Which of the following side effects is correct about Sandimmun Neoral®?

A) Nephrotoxicity
B) Neurotoxicity
C) Hyperlipidemia
D) GI Disturbances

4) Myfortic® is better than CellCept® due to;

A) Minimize GI side effects
B) Delayed-release enteric-coated
C) Less Neurotoxicity
D) A and B

5) All of the following brands are available in oral and IV formulations, Except;

A) Prograf®
B) Sandimmun Neoral®
C) Myfortic®
D) A and B

Your Score No. of correct answers	1 ❑	2 ❑	3 ❑	4 ❑	5 ❑

Day 41

1) Which of the following is most likely to be in patients with chronic renal insufficiency?

A) Cyanocobalamin
B) Deferoxamine
C) Folic Acid
D) Erythropoietin

2) Which of the following iron formulation can be taken in a single visit?

A) Ferumoxytol
B) Ferric Carboxymaltose
C) Iron Isomaltoside

3) Which of the following cobalamin can penetrate blood-brain barrier without assistance or conversion?

A) Cyanocobalamin
B) Hydroxocobalamin
C) Methylcobalamin

4) Which of the following is a parenteral iron chelator?

A) Deferoxamine
B) Deferiprone
C) Deferasirox

5) Which of the following might be beneficial to reduce the frequency of painful crises in a patient with sickle cell disease?

A) Epoetin alfa
B) Filgrastim
C) Hydroxyurea
D) Sargramostim

Your Score No. of correct answers	1	2	3	4	5
	❑	❑	❑	❑	❑

Day 42

1) All of the following are cytotoxic drugs, Except;

A) Monoclonal Antibodies
B) Antimetabolites
C) Alkylating Agents
D) Microtubule Inhibitors

2) Which of the following anticancer is oral prodrug?

A) Cytoxan®
B) Xeloda®
C) Leukeran®
D) None of the above

3) Syndrome of Inappropriate Secretion of Antidiuretic Hormone (SIADH) are associated with;

A) Anthracyclines
B) Platinum Salts
C) Taxanes
D) Vinca Alkaloids

4) Pravotin® is a

A) Oral Ferrous Sulfate
B) Parenteral Iron
C) Transferrin proteins
D) Bovine Lactoferrin

5) Oprelvekin (Neumega®) is a

A) Recombinant interleukin-1
B) Recombinant interleukin-6
C) Recombinant interleukin-11
D) None of the above

Your Score No. of correct answers	1	2	3	4	5
	❑	❑	❑	❑	❑

Day 43

1) Which of the following is correct diagnosis regarding to photo?

A) Acne vulgaris

B) Cystic acne

C) Acne Rosacea

2) Which of the following is correct diagnosis regarding to photo?

A) Acne scars

B) Acne Hyperpigmentation Spots

C) Acne Red Spots

3) Which of the following is correct diagnosis regarding to photo?

A) Skin Aging

B) Isotretinoin Therapy

C) Fatty acid deficiency

4) Which of the following is correct diagnosis regarding to photo?

A) Sunburn

B) Erysipelas

C) Stasis dermatitis

5) Which of the following is correct diagnosis regarding to photo?

A) Before and after Botox

B) Before and after Phototherapy

C) Before and after Laser therapy

Your Score No. of correct answers	1	2	3	4	5
	❑	❑	❑	❑	❑

Day 44

1) Which of the following is correct diagnosis regarding to photo?

A) Impetigo

B) Canker Sore

C) Cold Sore

2) Which of the following is correct diagnosis regarding to photo?

A) Dermatitis

B) Shingles

C) Erysipelas

3) Which of the following is correct diagnosis regarding to photo?

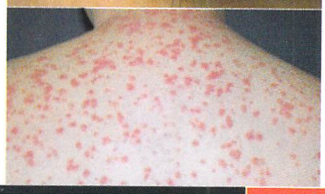
A) Lipodermatosclerosis

B) Erysipelas

C) Cellulitis

4) Which of the following is correct diagnosis regarding to photo?

A) Filiform wart
B) Common wart
C) Plantar Wart



5) Which of the following is correct diagnosis regarding to photo?

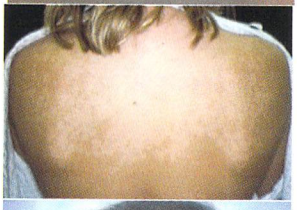
A) Dermatitis
B) Skin Rash
C) Guttate psoriasis

Your Score No. of correct answers	1 ❑	2 ❑	3 ❑	4 ❑	5 ❑

Day 45

1) Which of the following is correct diagnosis regarding to photo?

A) Tinea Corporis
B) Pityriasis Rosea
C) Tinea Versicolor



2) Which of the following is correct diagnosis regarding to photo?

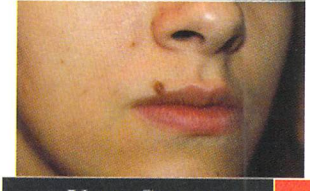
A) Tinea Corporis
B) Vitiligo
C) Tinea Versicolor

3) Which of the following is correct diagnosis regarding to photo?

A) Alopecia Areata
B) Telogen effluvium
C) Anagen effluvium

4) Which of the following is correct diagnosis regarding to photo?

A) Tinea Barbae
B) Tinea Cruris
C) Tinea Capitis



5) Which of the following is correct diagnosis regarding to photo?

A) Moles
B) Freckle
C) Skin Tag

Your Score No. of correct answers	1 ❑	2 ❑	3 ❑	4 ❑	5 ❑

Answers Table

	1	2	3	4	5		1	2	3	4	5
Day 1	B	D	D	B	B	Day 24	B	A	D	A	B
Day 2	A	B	A	B	A	Day 25	C	A	D	B	B
Day 3	A	C	D	A	E	Day 26	D	D	B	A	B
Day 4	A	D	B	A	C	Day 27	A	B	B	B	C
Day 5	B	B	C	D	A	Day 28	D	C	D	B	A
Day 6	D	A	D	E	A	Day 29	A	C	B	A	B
Day 7	A	B	C	D	A	Day 30	A	D	D	A	D
Day 8	D	D	D	A	C	Day 31	B	B	C	A	D
Day 9	D	A	A	A	C	Day 32	B	D	C	D	B
Day 10	B	C	B	D	A	Day 33	A	B	D	A	C
Day 11	A	D	C	A	B	Day 34	C	D	D	A	D
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Day 14	D	B	C	A	B	Day 37	D	A	D	B	A
Day 15	D	A	A	B	B	Day 38	C	A	B	A	B
Day 16	C	B	A	D	B	Day 39	B	A	C	B	A
Day 17	D	A	D	A	A	Day 40	D	A	A	D	C
Day 18	A	A	C	B	D	Day 41	D	C	C	A	C
Day 19	D	B	B	A	A	Day 42	A	B	D	D	C
Day 20	D	A	E	A	A	Day 43	B	A	B	A	A
Day 21	D	B	B	D	B	Day 44	A	B	A	A	C
Day 22	B	B	A	A	D	Day 45	B	C	C	B	A
Day 23	D	C	B	B	C						

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List of Medical Abbreviations Used in Index

g; Generation

ACEI; Angiotensin-Converting Enzyme Inhibitor

ACTH; Adrenocorticotropic Hormone

ARB; Angiotensin II Receptor Blocker

ARNI; Angiotensin-Receptor Neprilysin Inhibitor

CAI; Carbonic Anhydrase Inhibitor

CCB; Calcium Channel Blocker

COMT; Catechol-O-Methyltransferase

GnRH; Gonadotropin-releasing Hormone

G-CSF; Granulocyte Colony–Stimulating Factors

SGLT; Sodium/Glucose Co-transporter

DPP-4; Dipeptidyl Peptidase-4

mTOR; Mechanistic Target Of Rapamycin

SURI; Selective Uric acid Reabsorption Inhibitor

mAb; Monoclonal Antibody

MAOI; Monoamine Oxidase Inhibitor

NMDA; N-Methyl-D-Aspartate

NRI; Norepinephrine Reuptake Inhibitor

SERM; Selective Estrogen Receptor Modulator

SNRI; Serotonin/Norepinephrine Reuptake Inhibitor

SPRM; Selective Progesterone Receptor Modulator

SSRI: Selective Serotonin Reuptake Inhibitor

GM-CSF; Granulocyte Macrophage Colony-Stimulating Factor

NK1; Neurokinin 1

TKI; Tyrosine Kinase Inhibitor

HDAC; Histone Deacetylase Inhibitor

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